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Real-world outcomes of patients receiving prophylactic therapies for hepatic encephalopathy

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Real-world outcomes of patients receiving prophylactic therapies for hepatic encephalopathy

by

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Abstract

Real-world outcomes of patients receiving prophylactic therapies for hepatic encephalopathy

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Background: Hepatic encephalopathy (HE) is a reversible complication of liver disease characterized by neuropsychiatric abnormalities ranging from mild cognitive impairment to coma. Several strategies, including prophylaxis with rifaximin and/or lactulose are recommended to prevent HE recurrence. While efficacy of rifaximin compared to placebo was demonstrated in clinical trials, there is limited evidence confirming real-world effectiveness.

Objective: To assess the real-world effectiveness of rifaximin as prophylaxis for HE.

Methods: This observational, retrospective, cohort study utilized existing electronic health record data at a large integrated delivery network (IDN) in Texas (2014–2020). Patients were indexed on the date of discharge from the first eligible HE-related hospitalization during the enrollment period and grouped based on the presence or absence of an active, outpatient medication order for rifaximin at discharge. Patient characteristics, comorbidities, labs, flowsheet data, and medication orders were collected at baseline.

Logistic regression was used to generate propensity scores (PS) and match patients to treatment groups. Proportions of patients with hospitalizations or emergency department (ED) visits classified by cause (HE-, liver-related, and/or all-cause) and time (30- and/or 180-days post-index), and mortality were compared between treatment groups.

Results: A total of 1,541 patients met all study criteria (N=390, rifaximin; N=1,151, control), of which 694 patients were PS-matched to treatment groups (N=347, both). Analysis of the PS-matched cohort showed no statistically significant differences between rifaximin and control in hospitalizations at 180 days (all: 58% vs. 56%, *P*=0.6451; liver: 58% vs. 55%, *P*=0.5402; HE: 32% vs. 32%, *P*=0.9352), and 30 days (all: 31% vs. 29%, *P*=0.6191; liver: 30% vs. 29%, *P*=0.6171; HE: 14% vs. 14%, *P*=0.9128), or ED visits at 180 days (all: 63% vs. 62%, *P*=0.7534; liver: 60% vs. 57%, *P*=0.5381; HE: 26% vs. 28%, *P*=0.4930) and 30 days (all: 35% vs. 35%, *P*=0.8113; liver: 33% vs. 31%, *P*=0.5675; HE: 12% vs. 12%, *P*=0.8141), or mortality rates (19% vs. 20%; *P*=0.7723).

Conclusion: After controlling for measurable covariates, patients discharged from an HE-related hospitalization experienced no statistically significant differences in all-cause, liver-related, or HE-related hospitalizations, ED visits at 30 or 180 days, or mortality with vs. without a rifaximin order at discharge.

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Chapter 1: Introduction

DISEASE OVERVIEW

Introduction and Epidemiology

Hepatic encephalopathy (HE) is a reversible complication of liver disease characterized by a spectrum of neuropsychiatric abnormalities ranging from mild cognitive impairment to life-threatening presentations, including coma. While HE poses a substantial burden to patients and caregivers, progress in treatment and prevention of the disease has been hindered by its complex pathogenesis.[1] With mild cases often undiagnosed, the exact incidence of HE in the US is unknown and varies substantially based on the presence of risk factors. Within five years of diagnosis of cirrhosis, the risk for an initial episode of overt HE has been found to be between 5–25%,[2-6] and patients with a previous episode of overt HE have a 40% cumulative risk for recurrence.[7] Patients with transjugular intrahepatic portosystemic shunt (TIPS) are also at high risk of HE, with a median cumulative one-year incidence between 10–50%.[8-9] The overall incidence of HE among Medicare enrollees with cirrhosis was found to be 11.6 per 100 patient-years.[10]

Pathophysiology

The etiology of HE is hypothesized to be multifactorial in nature, with excess presence of ammonia historically being considered as the main factor leading to HE. Ammonia is produced predominantly by colonic bacterial species with urease enzyme activity (e.g., *Enterobacteriaceae*, *Proteus,* and *Clostridium* species). Bacterial urease leads to the breakdown of urea in the bloodstream into ammonia and carbon dioxide.[11] Alternatively, enterocytes in the small bowel can also generate ammonia via intestinal glutaminase.[12] In healthy patients, ammonia generated by bacteria and enterocytes travels

to the liver for metabolism following the urea cycle in zone 1, which is then excreted as urea by the kidneys.[11] However, in patients with liver disease, metabolism by the liver can be reduced and compounded by the shunting of blood away from the liver.[13] In patients with HE, significant correlations between plasma ammonia levels, cerebral ammonia metabolism and magnetic resonance spectroscopy (MRS) alterations in white matter have been observed.[14] Several mechanisms for ammonia toxicity have been proposed, primarily focused on astrocytes in the brain. For instance, metabolism of ammonia to glutamine by astrocytes can lead to increased intracellular osmolarity and cerebral edema, resulting in neuronal dysfunction and the manifestation of HE-related symptoms.[11]

In addition to ammonia, other molecules have also been implicated in the pathogenesis of HE. Neurosteroids (e.g., allopregnanolone) modulate gamma-aminobutyric acid (GABA)-A receptors, in a similar manner as benzodiazepines, which can also lead to astrocyte swelling.[11] Indole and oxindole, which have sedating properties, have also been implicated in the pathogenesis of HE.[11] Additional mechanisms involving acetylcholinesterase (AChE), hyponatremia, mercaptans, short-chain fatty acids, false neurotransmitters, manganese, and GABA have also been identified.[11]

Inflammation and infection (with systemic inflammatory response syndrome) have also been associated with HE. Increased levels of the pro-inflammatory cytokines tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-1B have been found to act synergistically with ammonia in causing cerebral edema.[15]

Clinical Presentation

HE manifests in a wide spectrum of neurological and psychiatric abnormalities, ranging from subclinical alterations to coma.[1] Minimal HE may only result in minor changes in attention, memory, movement, or vision.[16] However, progression of HE can

lead to several psychiatric and neurological symptoms, such as personality changes, excessive daytime sleepiness, disorientation to time and space, inappropriate behavior, confusion, and coma.[17-18] Asterixis, also known as a flapping tremor, is a commonly observed motor symptom in patients with HE, and is used in the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus for classifying the episode as 'overt' or 'covert'. Other motor symptoms include hypertonia, hyper-reflexia, positive Babinski sign, and extrapyramidal dysfunction.

Prognosis and Burden of Illness

HE is associated with poor health outcomes and high economic burden. Data analyzed from the US Nationwide Inpatient Sample (NIS) from 2005 to 2009 showed that the yearly mortality rate for patients hospitalized with HE ranged from 14.1 to 15.6%, and the average length of inpatient stay was 8.1 to 8.5 days.[19] According to separate analysis of NIS data from 2004 to 2014, HE-related hospitalizations increased annually from 95,232 in 2004 to 156,205 in 2014.[20] Cost data was reported in the analysis for 55,485 hospitalizations in 2014, with an unadjusted total cost of approximately $620 million total (or $11,174 per hospitalization) for the sample.[20]

Impaired health-related quality of life (HRQoL) is also a major consequence of HE. In a sample of 160 patients presenting for liver transplantation, average HRQoL scores, as measured through the Short Form (SF)-36 questionnaire, decreased in the physical component summary (29.3 vs. 35.6, P=0.018) and mental component summary (44.0 vs. 50.0, P=0.03) in patients with vs. without HE.[21]

CLINICAL PRACTICE GUIDELINES

Evaluation

Guidelines from the American Association for the Study of Liver Diseases (AASLD) published in 2014 recommend that providers caring for patients with HE consider the nature of the underlying disease, timing, presence or absence of precipitating factors, and symptom severity. There are three types of underlying disease: 'Type A' (patients with acute liver failure), 'Type B' (patients with bypass shunts), and, most commonly, 'Type C' (patients with chronic liver disease).[1] In patients with Type B or C, patterns of HE may be described as 'minimal' (exhibiting no outward signs or symptoms in a typical clinical setting), 'episodic' (occurring at intermittent periods with or without an identifiable precipitating factor), 'recurrent' (time intervals of six months or less), or 'persistent' (ongoing deficit in neuropsychological functioning).

Patients that present with clinically apparent HE are typically classified on a four-point scale following the West Haven Criteria, also known as the Conn Score.[1] Guidelines recommend that every case be described and classified according to all four factors and repeated at relevant intervals. Classification based on West Haven Criteria is described in Table 1.1 below:

West Haven Criteria / Conn Score	ISHEN	Description	Suggested Operative Criteria
Unimpaired		No encephalopathy or history of HE	Tested and proved to be normal
Minimal	Covert	Alterations of tests exploring psychomotor speed, executive functions, or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established tests without clinical manifestations
Grade I		Trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, or altered sleep rhythm	Oriented in time and space, but some cognitive or behavior decay on clinical or with caregivers
Grade II	Overt	Lethargy or apathy, disorientation for time, obvious personality change, inappropriate behavior, dyspraxia, asterixis	Disoriented for time ± the other mentioned symptoms
Grade III		Somnolence to semistupor, responsive to stimuli, confused, gross disorientation, bizarre behavior	Disoriented also for space ± the other mentioned symptoms
Grade IV		Coma	Does not respond even to painful stimuli

Table 1.1: West Haven Criteria and Clinical Description [Adapted][1]

For patients with liver disease, prognostic models have been utilized to estimate mortality for prioritization of organ allocation for transplantation. The Model for End-stage Liver Disease (MELD) score is a validated system for chronic liver disease severity

scoring.[22] It was originally developed to predict three-month mortality following TIPS placement,[23] but has been used for all patients with chronic liver disease given its strength in predicting survival and mortality. The score includes three laboratory values: serum bilirubin [mg/dL], international normalized ratio (INR), and serum creatinine (SCr) [mg/dL]. Scores typically range from 6 to 40, with large increases commonly seen during periods of infection or acute decompensation. Mortality rates at three months for patients with chronic liver disease by MELD scores are summarized in Table 1.2 below:

MELD Score*	3-month Mortality Rate
<9	1.9%
10 to 19	6.0%
20 to 29	19.6%
30 to 39	52.6%
>40	71.3%

* MELD = 3.8*ln(bilirubin) + 11.2*ln(INR) + 9.6*ln(SCr) + 6.4

Table 1.2: 3-month Mortality Rates by MELD Score[24]

Treatments

Patients with a history of overt HE are at high risk of recurrent episodes. Several strategies are recommended to prevent recurrent episodes of HE, including control of precipitating factors, nutritional support, and pharmacologic therapies to lower blood ammonia, specifically nonabsorbable disaccharides (e. g. lactulose) and rifaximin.[1]

Nonabsorbable Disaccharides

Lactulose (brand: Constulose®, Enulose®, Generlac®, Kristalose®) is indicated for the prevention and treatment of portal-systemic encephalopathy[25] and is considered first-line for the treatment and prevention of overt HE.[1] Upon oral administration, it is degraded by intestinal bacteria, resulting in an acidic pH. This leads to conversion of NH_3 to NH_4^+,

thereby inhibiting diffusion of ammonia into the bloodstream. Lactulose also enhances the diffusion of NH_3 from the blood into the gut, where it is again converted to NH_4^+. Additionally, lactulose produces an osmotic effect in the colon, and is commonly used for the treatment of constipation.

For HE prophylaxis, 30 to 45 mL of lactulose is administered between three to four times per day, titrated to achieve two to three soft stools per day. In an open-label trial of patients with cirrhosis who recovered from a previous episode of HE (N=140), 12 of 61 (19.6%) patients treated with lactulose experienced a subsequent HE, compared to 30 of 64 (46.8%) who were not treated with lactulose (P=0.001).[7] Adverse effects of lactulose reported in the study were diarrhea (23%), bad taste (13%), and abdominal bloating (10%). Additionally, lactulose can cause dehydration, electrolyte imbalances, nausea, vomiting, flatulence, and abdominal cramps/distress.

Lactulose is available in the US by prescription only at a relatively low cost. As of October 2020, the average wholesale price (AWP) for a 473 mL package size of lactulose is $34.70 to $40.15, which corresponds to an AWP per 30-day supply of $198 to $458, depending on the prescribed dose and frequency of use.[26]

Rifaximin

Rifaximin (brand: Xifaxan®) is an antibiotic indicated to reduce the risk of overt HE recurrence in adults.[27] Its mechanism of action occurs through binding to the beta-subunit of bacterial DNA-dependent RNA polymerase, thereby inhibiting bacterial protein synthesis. It has a broad spectrum of activity against gram-positive and gram negative, aerobic and anaerobic, enteric bacteria, and poorly absorbed, with 97% excretion through feces unchanged. Additionally, rifaximin is indicated for the treatment of travelers' diarrhea (TD) and irritable bowel syndrome with diarrhea (IBS-D).

Efficacy for rifaximin was established in a randomized, double-blind, placebo-controlled trial (Bass et al., 2010)[28] of patients with at least two prior episodes of HE associated with chronic liver disease in the previous six months but were in remission (Conn score of 0 or 1) at baseline. Patients (mean age 56 years, age range 21–82 years, 61% male, 86% white) included in the study (N=299) were randomized to receive rifaximin 550 mg twice daily (n=140), or placebo (n=159). Lactulose was used concomitantly in 91% of patients. MELD scores at baseline were between 11–18 for 64% of patients, and no patients had a MELD score >25. Breakthrough overt HE episodes, defined as an increase of Conn score ≥2, occurred in 31 (22%) patients that received rifaximin compared to 73 (46%) patients that received placebo during the six-month study period (P<0.0001). HE-related hospitalizations, defined as hospitalizations directly resulting from HE or hospitalizations complicated by HE, occurred in 19 (14%) of patients receiving rifaximin compared to 36 (23%) patients receiving placebo (P=0.0129). Adverse events occurring at over 5% and at a higher rate in the rifaximin vs. placebo group included peripheral edema (15% vs. 8%), dizziness (13% vs. 8%), pruritus (9% vs. 6%), anemia (8% vs. 4%), arthralgia and pyrexia (6% vs. 3%, each). Death occurred in 9 (6.4%) patients in the rifaximin group and 11 (6.9%) in the placebo group.

The AWP of rifaximin 550 mg is $3,066.71 for 60 capsules (30-day supply), considerably higher than for a 30-day supply of lactulose. However, there are studies demonstrating cost-effectiveness of rifaximin compared to lactulose, which are described in more detail later in this chapter.[29]

Follow-up

Upon discharge from a hospital admission, guidelines recommend that the medical team confirm neurological status, recognize precipitating factors, and provide discharge

consultation to prevent reappearance of precipitating factors.[1] Education of patients, relatives and caregivers is essential for prevention, and should consist of medication effects, importance of adherence, signs of recurrent HE, and actions to be taken in case of recurrence.[1] Underlying liver pathology in some patients can improve with time and nutrition, though most patients with a previous overt HE episode have advanced liver failure that will not result in functional improvement.[1] Adequate intake of protein to increase muscle mass is recommended, as weight loss with sarcopenia may worsen HE.[1]

LITERATURE REVIEW ON THE USE OF RIFAXIMIN AS PROPHYLAXIS FOR HEPATIC ENCEPHALOPATHY

Observational Studies

Hammond et al. (2017)[30] conducted a retrospective cohort study using a 10% random sample of medical and pharmacy claims from the IMS LifeLink PharMetrics Plus database between January 2006 and June 2015 (N=606). Patients were divided into two treatment groups – lactulose plus rifaximin (n=169) vs. lactulose only (n=437) – and followed for six months following an initial overt HE event. No difference in hospitalization for HE was observed between treatment groups (16.0% vs. 15.3%, *P*=0.841). Further adjustment for confounders also did not show a statistically significant difference in risk for an overt HE event (HR: 1.05, 95% CI [0.81, 1.28]). Of note, results are only available in abstract, and the authors acknowledge that findings may be due to residual, unobserved confounding.

Courson et al. (2015)[31] retrospectively reviewed electronic health record (EHR) data in hospitalized patients admitted for HE to a single hospital in Tennessee between 2007 and 2012. Of the entire study population (N=173), 110 patients were eligible for

analysis of hospital readmission rates. Patients were grouped by treatment received while in the hospital – lactulose only (n=68), lactulose plus rifaximin (n=42). Of note, two patients (2.9%) in the lactulose only group were discharged with a prescription for rifaximin compared to 25 (59.5%) in the lactulose plus rifaximin group. HE-related admissions observed at 180 days were significantly lower in patients in the lactulose plus rifaximin group (n=1, 2.4%) compared to lactulose monotherapy (n=11, 16.2%, *P*=0.028). However, there were no statistically significant differences found in HE-related readmissions at 30 days, and all-cause readmissions at 30 and 180 days.

Vadhariya et al. (2020)[32] conducted a retrospective analysis of claims data in Medicare patients in Texas who were hospitalized and recovered from HE from January 2011 to May 2018 (N=184). Overall, medication use at discharge was identified in 117 (63.5%) patients, with only 9 (4.9%) receiving rifaximin. Adherence rates, measured through proportion of days covered (PDC), were relatively low in this population, ranging from 0.56 to 0.82 at three months and 0.48 to 0.77 at six months.

Hudson et al. (2017)[33] conducted a retrospective, cross-sectional study in patients with HE that received care at multiple hospitals across the UK between July 2008 and May 2014 (N=114). Statistically significant reductions in the mean number of liver-related and all-cause hospitalizations were observed in the six months following initiation of rifaximin, compared to the previous six months (liver-related: 1.3 vs. 0.5, *P*<0.001; all-cause: 1.9 vs. 0.9, *P*<0.001). Similar reductions in the mean numbers of hospital bed days, 30-day hospital readmissions, and emergency department (ED) visits were also observed.

Kang et al. (2017)[34] evaluated patients at a single tertiary hospital in South Korea who recovered from HE between January 2010 and June 2015 (N=1,042). In patients without hepatocellular carcinoma (HCC), those who received rifaximin plus lactulose (n=145) had a significantly lower risk of recurrent HE (HR: 0.452, *P*=0.001) and death

(HR: 0.697, *P*=0.24) compared to patients that only received lactulose (n=276). However, there was not a statistically significant difference between treatment groups in the rate of recurrent HE in patients with HCC (HR: 0.689, *P*=0.57).

Pharmacoeconomic Analysis

Jesudian et al. (2020)[35] assessed the incremental cost-effectiveness of rifaximin (with and without lactulose) compared to control (also, with and without lactulose) in patients with HE. Costs and outcomes were evaluated using a Markov model. The model predicted the course of HE upon initiation of maintenance therapy to avoid recurrent HE episodes over a lifetime horizon. Four health states were modeled, as shown in Figure 1.1: (1) remission, (2) overt HE (with or without hospitalization), (3) transplant, and (4) death. Patients start in remission and are eligible to transition to each of the different health states every two weeks. Liver transplantation and death are both considered to be exit states.

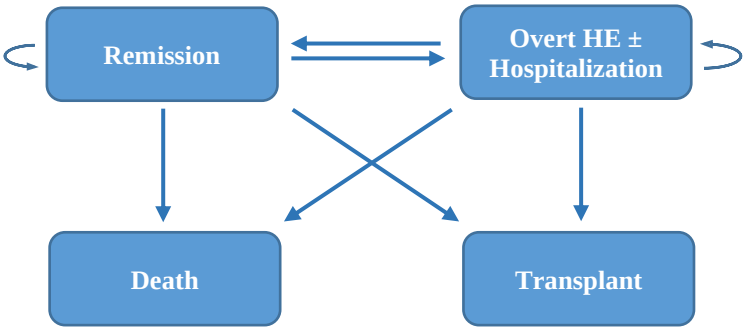


Figure 1.1: Cost-effectiveness Model Structure [Adapted][35]

Inputs for the cost-effectiveness model are summarized in Table 1.3. Data sources for the clinical modeling inputs include the 6-month pivotal clinical trial (Bass et al., 2010[28]), the 24-month open-label maintenance study (Mullen et al., 2014[36]), and a randomized controlled trial of hospitalized patients (Sharma et al., 2013[37]). HE-related

health utilities were estimated using interviewer-administered time trade-off and standard gamble utilities from a random sample of subjects in the UK (Guest et al., 2014[38]). Hospitalization costs were estimated from several data sources and adjusted to 2018 US dollars.

Input	Rifaximin	Control	Source
On concomitant lactulose	91.4%	91.2%	Bass et al., 2010[28]
Remission state			
With overt episodes at 6 months	22.1%	45.9%	Bass et al., 2010[28]
Hospitalizations per person-years	0.24	0.58	Mullen et al., 2014[36]
Mortality at year 5	52.8%	59.9%	Mullen et al., 2014[36]
Health utility	0.937		Guest et al., 2014[38]
Overt HE state			
Hospitalized	61.5%	49.2%	Bass et al., 2010[28]
Reversed after 2 weeks (hospital)	76.0%	44.0%	Sharma et al., 2013[37]
Mortality after 2 weeks (in-hospital)	23.8%	49.1%	Sharma et al., 2013[37]
Mortality after 2 weeks (post-hospital)	0.6%	0.9%	Mullen et al., 2014[36]
Mortality after 2 weeks (non-hospital)	0.6%	0.9%	Mullen et al., 2014[36]
Health utility	0.783		Bass et al., 2010,[28] Guest et al., 2014[38]
Transplant state			
Transplants per patient per year	0.061		Mullen et al., 2014[36]
Life expectancy after transplant	29.3 year		Kim et al., 2018[39]
Health utility	0.962		Guest et al., 2014[38]
Costs			
HE-related hospitalization	$19,710	$24,527	Multiple
Non-HE-related hospitalization	$15,892		Multiple
Liver transplantation	$183,132		Multiple

Table 1.3: Cost-Effectiveness Model Inputs [Adapted][35]

The model estimated 6.4 quality-adjusted life years (QALY) per patient receiving rifaximin at a total cost of $152,406, compared to 3.1 QALYs per patient in the control

group at a total cost of $56,031. As such, the incremental cost per QALY from the addition of rifaximin was $29,161.

STUDY RATIONALE

Knowledge Gaps

Bass et al. (2008)[28] demonstrated that rifaximin was substantially superior to lactulose for the prevention of recurrent HE-related hospitalizations; however, there is limited evidence confirming the real-world effectiveness of rifaximin as prophylaxis. In a recent literature review on evidence of long-term management of HE with lactulose and/or rifaximin,[40] the authors discussed the limited availability of direct head-to-head evidence to support rifaximin over lactulose. In addition to the lack of effectiveness observed in Hammond et al. (2017),[30] conflicting evidence in the efficacy of rifaximin as observed in a single-center, randomized controlled trial[41] has also raised speculation of different outcomes occurring in patients with an etiology of cirrhosis, or different geographical and dietary backgrounds.[40]

Decreases in direct costs due to HE-related hospital admissions and ED visits are needed to offset the high drug cost of rifaximin relative to lactulose. While cost-effectiveness has been demonstrated using inputs sourced from clinical trials, application of real-world evidence to economic analyses remains limited.

Purpose

This study assesses the real-world effectiveness of rifaximin as prophylaxis for HE using electronic health record (EHR) data at Baylor Scott & White Health (BSWH), a large integrated health system in Central and North Texas. BSWH is comprised of 52 hospitals

and over 800 patient access points, with more than 7.5 million patient encounters, 900,000 ED visits, and 200,000 hospital admissions occurring at BSWH, annually.[42] Results from this analysis can be used to better inform existing cost-effectiveness models. The methods used within this analysis can also be shared as a framework for additional analyses at other health systems.

Chapter 2: Methods

OBJECTIVES AND HYPOTHESES

The aim of the study was to evaluate the effectiveness of rifaximin used as prophylaxis for hepatic encephalopathy (HE) at BSWH. Effectiveness was measured through healthcare utilization metrics related to hospitalizations and emergency department (ED) visits. The full list of objectives and hypotheses are summarized in Table 2.1 below:

Objective 1: To evaluate the baseline characteristics of patients following the first qualifying episode of HE.
• H_0 1.1: The difference in patient age between treatment groups is not statistically significant. • H_0 1.2: The difference in proportions of patients by age category between treatment groups is not statistically significant. • H_0 1.3: The difference in proportions of patients by gender between treatment groups is not statistically significant. • H_0 1.4: The difference in proportions of patients by race category between treatment groups is not statistically significant. • H_0 1.5: The difference in proportions of patients by ethnicity between treatment groups is not statistically significant. • H_0 1.6: The difference in proportions of patients by primary insurance type between treatment groups is not statistically significant. • H_0 1.7: The differences in proportions of patients with select comorbidities[i] at baseline between treatment groups are not statistically significant. • H_0 1.8: The difference in patient comorbidity index between treatment groups is not statistically significant. • H_0 1.9: The differences in individual laboratory measurements[ii] at baseline between treatment groups are not statistically significant. • H_0 1.10: The difference in proportions of patients by MELD score category[iii] at baseline between treatment groups is not statistically significant. • H_0 1.11: The difference in proportions of patients by Glasgow Coma Scale category[iv] at baseline between treatment groups is not statistically significant. • H_0 1.12: The difference in proportions of patients by prior medication use[v] between treatment groups is not statistically significant.

- H_0 1.13: The difference in length of stay at baseline between treatment groups is not statistically significant.
- H_0 1.14: The difference in proportion of patients with active lactulose orders at baseline between treatment groups is not statistically significant.

[i] Comorbidities = cirrhosis, hepatocellular carcinoma, hepatitis B, hepatitis C, non-alcoholic fatty liver disease (NAFLD), alcohol abuse, diabetes, and renal failure

[ii] Laboratory measurements = SCr, bilirubin, INR, serum aminotransferase levels (e.g. AST, ALT), ammonia, and white blood cell count (WBC). WBC was categorized as elevated (>11,000 cells per µl of blood, or not elevated).

[iii] MELD score values were categorized as ≤5, 6–10, 11–15, 16–20, 21–25, 26–30, or ≥31

[iv] Glasgow Coma Scale values were categorized as mild (13–15), moderate (9–12), and severe (3–8)

[v] Prior medications = rifaximin, lactulose

Objective 2: To compare healthcare utilization metrics in patients that did or did not receive rifaximin following the first qualifying episode of HE.

- H_0 2.1: The difference in proportions of patients with at least one all-cause hospitalization at 180 days between treatment groups is not statistically significant.
- H_0 2.2: The difference in proportions of patients with at least one liver-related hospitalization at 180 days between treatment groups is not statistically significant.
- H_0 2.3: The difference in proportions of patients with at least one HE-related hospitalization at 180 days between treatment groups is not statistically significant.
- H_0 2.4: The difference in proportions of patients with at least one all-cause hospitalization at 30 days between treatment groups is not statistically significant.
- H_0 2.5: The difference in proportions of patients with at least one liver-related hospitalization at 30 days between treatment groups is not statistically significant.
- H_0 2.6: The difference in proportions of patients with at least one HE-related hospitalization at 30 days between treatment groups is not statistically significant.
- H_0 2.7: The difference in proportions of patients with at least one all-cause ED visit at 180 days between treatment groups is not statistically significant.
- H_0 2.8: The difference in proportions of patients with at least one liver-related ED visit at 180 days between treatment groups is not statistically significant.
- H_0 2.9: The difference in proportions of patients with at least one HE-related ED visit at 180 days between treatment groups is not statistically significant.
- H_0 2.10: The difference in proportions of patients with at least one all-cause ED visit at 30 days between treatment groups is not statistically significant.
- H_0 2.11: The difference in proportions of patients with at least one liver-related ED visit at 30 days between treatment groups is not statistically significant.
- H_0 2.12: The difference in proportions of patients with at least one HE-related ED visit at 30 days between treatment groups is not statistically significant.
- H_0 2.13: The difference in time to first all-cause hospitalization between treatment groups is not statistically significant.

• H_0 2.14: The difference in time to first liver-related hospitalization between treatment groups is not statistically significant. • H_0 2.15: The difference in time to first HE-related hospitalization between treatment groups is not statistically significant. • H_0 2.16: The difference in time to first all-cause ED visit between treatment groups is not statistically significant. • H_0 2.17: The difference in time to first liver-related ED visit between treatment groups is not statistically significant. • H_0 2.18: The difference in time to first HE-related ED-visit between treatment groups is not statistically significant.
Objective 3: To assess the accuracy of using EHR data to define medication use in patients prescribed rifaximin as prophylaxis for HE.
• H_0 3.1: The difference in proportions of patients with rifaximin ordered vs. filled data is not statistically significant. • H_0 3.2: The difference in proportions of patients with rifaximin ordered vs. proportion of days covered by rifaximin ≥80% is not statistically significant.

Table 2.1: Study Objectives and Hypotheses

STUDY DESIGN

The study followed an observational, retrospective, cohort design, utilizing existing data from the electronic health record (EHR) at BSWH. The study was approved by the Institutional Review Boards at BSWH (expedited review) and the University of Texas at Austin (exempt).

As shown in Figure 2.1, data were collected during the study period from January 1, 2014 to Dec 31, 2020. A baseline period of 6 months was used to ensure no prior recent history of HE-related hospitalizations. Patients were then followed for 6 months post-index and assessed for study outcomes of interest.

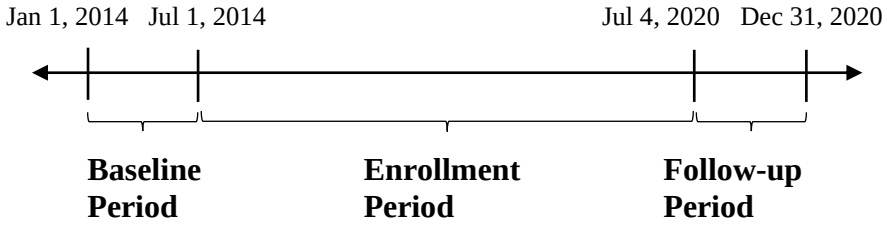


Figure 2.1: Study Design

POPULATION

Patients were enrolled into the study on the index date, defined as the discharge date from the first eligible HE-related hospitalization during the enrollment period. Eligibility criteria for HE-related hospitalizations were defined through several inclusion and exclusion criteria as described in Table 2.2 below:

Inclusion Criteria	Exclusion Criteria
• Discharged from an HE-related hospitalization during the study enrollment period to home (with home health, or self-care) or an assisted living facility (long term acute care, nursing facility, rehab facility, skilled nursing facility or custodial care facility) • Age ≥18 years at index date • Sufficient laboratory data during the first eligible HE-related hospitalization to calculate a MELD score (e.g. SCr, bilirubin, and INR)	• No HE-related hospitalizations during the 6 months prior to the index date • Admitted to transplant or hospice service for first episode of HE • Discharged from the first episode of HE with planned inpatient acute care readmission, discharged to another hospital, hospice, court/law enforcement, or left against medical advice • Deceased during the first episode of HE • Patients with insufficient laboratory results needed to calculate a MELD score during the first eligible HE-related hospitalization

Table 2.2: Study Criteria

Hospitalizations were considered to be HE-related if a diagnosis of HE (identified using ICD-9-CM and ICD-10-CM codes listed in Appendix A) was coded in any position or noted as the primary problem. A sensitivity analysis was conducted using different requirements for the position of the HE-related diagnosis code (e.g. all positions, first eight positions, first four positions, primary and secondary positions, or primary position only). Criteria related to discharge disposition was intended to capture patients that might receive the most benefit from prophylaxis with rifaximin. Patients were also required to have laboratory data (SCr, biliriubin, and INR) from the first HE-related hospitalization for baseline disease severity to be assessed.

Treatment Groups

Eligible patients were grouped based on the presence or absence of an active, outpatient medication order for rifaximin at discharge. However, medication orders are prescribing events that do not necessarily correlate with the prescribed medication being taken or even filled by the patient. In comparison, medication fills, which can be identified using pharmacy (Rx) claims data, allow for calculation of a proportion of days covered (PDC) ratio, which can more closely approximate medication use. An exploratory analysis was conducted on the subset of study patients enrolled in the Scott & White Health Plan (SWHP) comparing medication use identified through Rx claims data vs. EHR data.

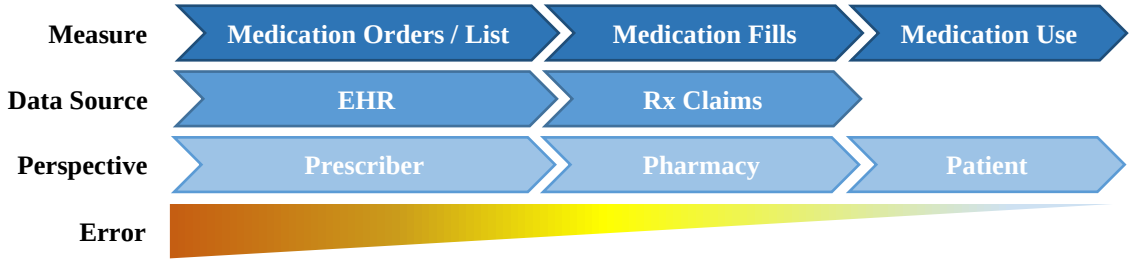


Figure 2.2: Available Methods for Assessing Medication Use in Retrospective Studies

DATA COLLECTION

Data were extracted from the BSWH EHR using EPIC Caboodle data model. Rx claims data for study patients continuously enrolled in the SWHP during the study period was extracted from the Virtual Data Warehouse (VDW). A full list of variables extracted from EPIC and the VDW are summarized in Table 2.3:

Category *(Data Source)*	**Variable**	**Criteria**
Patient Characteristics *(EPIC Caboodle)*	Identifier	• On the index date
	Birth date	
	Gender	
	Race	
	Ethnicity	
	Primary insurance	
Comorbidities *(EPIC Caboodle)*	Cirrhosis (all)	• Active on the patient's problem list during the first eligible HE-related hospitalization, or an outpatient encounter with a date between the 6-month pre-index date and the index date
	Cirrhosis (alcoholic)	
	Hepatocellular carcinoma	
	Hepatitis B	
	Hepatitis C	
	NAFLD/NASH	
	Alcohol abuse	
	Diabetes	
	Renal failure	
	Additional comorbidities for Elixhauser Comorbidity Index	
Laboratory / Flowsheet Data *(EPIC Caboodle)*	Serum creatinine (last)	• Measured during the qualifying episode of HE
	Bilirubin (last)	
	INR (last)	
	AST serum level (last)	
	ALT serum level (last)	
	Ammonia (first)	
	White blood cell count (first)	
	Glasgow Coma Scale (first)	
Medication List *(EPIC Caboodle)*	Medication name	• Order date between the 6-month pre-index date and 6-month post-index date
	Order date	
	Quantity	
	Refills	
	Start date	
	Stop date	
Hospitalizations *(EPIC Caboodle)*	Encounter key	• During the entire study period (eligibility) • Between the index date and 6 months post-index
	Admit date	
	Principal problem	
	Coded diagnosis	
	Diagnosis sequence number	
	Discharge date	
	Discharge disposition	
	Length of stay in days	
	Department location	

ED Visits *(EPIC Caboodle)*	Encounter key	Between the index date and 6 months post-index
	Encounter date	
	Chief complaint	
	Coded diagnosis	
	Diagnosis position number	
Mortality *(EPIC Caboodle)*	Identifier	Death date prior to the 6-month post-index date
	Death date	
Pharmacy claims *(VDW)*	Patient identifier	Date of service between the 6-months pre-index date and 6-months post-index date
	Medication name	
	Date of service	
	Quantity	
	Day supply	

Table 2.3: Study Variables

Patient characteristics including age, sex, race, ethnicity, and primary insurance type were collected at baseline. Patients with race recorded as 'American Indian or Alaska Native', 'Asian', 'Native Hawaiian or Other Pacific Islander', 'Puerto Rican', 'Other', and 'Some Other Race Only' were all re-categorized as 'Other' due to low sample sizes. Comorbidities were identified by searching for EHR diagnosis keys that map to ICD-9-CM or ICD-10-CM diagnosis codes (as detailed in Appendix A) that were either coded during the first eligible HE-related encounter, or active on the patient's problem list during an outpatient encounter between the 6-month pre-index date and the index date. Additionally, an Elixhauser Comorbidity Index (ECI) was calculated for each patient using Elixhauser Comorbidity Software, Version 3.7 from the Healthcare Cost and Utilization Project (HCUP).[43]

Laboratory data from the first eligible HE-related encounter were also collected to describe and characterize patients' disease severity at baseline. The last measurement in the encounter was used for each of the components of the MELD score (SCr, bilirubin, and INR), whereas the first measurement in the encounter was used for ammonia and WBC count. MELD scores were then calculated for each patient at baseline. Additionally, a

cutoff of >11,000 cells per μl of blood was used to define categorize WBC values as elevated or not elevated. The first measurement of the Glasgow Coma Scale scaled score during the first eligible HE-related encounter was collected from flowsheet data. Lastly, length of stay (LOS) of the first eligible HE-related encounter was reported in days.

OUTCOME MEASURES

The primary effectiveness outcome measure for the study was the proportion of patients with at least one hospital admission during the post-index study period by treatment group (rifaximin vs. no rifaximin). Hospital admissions were categorized by coded diagnoses as being HE-related, liver-related, and/or all-cause, with a sensitivity analysis performed based on the positioning of the diagnosis code used to define a hospitalization as HE- or liver-related. Outcomes occurring within 30 days and/or 180 days post-index were assessed. Time (in days) to first hospital admission was also collected and reported separately based on the reason for admission (all-cause, liver-related, HE-related).

As a secondary outcome measure, emergency department (ED) visits were collected and reported in a similar manner as hospital admissions. Coded diagnoses were used to categorize ED visits as HE-related, liver-related and/or all-cause. Results were reported as proportions of patients with at least one ED visit in each of the respective categories (all-cause, liver-related, HE-related) and time periods (30 days, 180 days).

All-cause mortality data was also collected from the EHR and reported as an outcome measure. Counts and proportions of patients that died during the 180 days post-index were reported, along with a survival analysis.

Two exploratory endpoints were used to measure rifaximin medication fills from pharmacy claims data in the subset of study patients with SWHP insurance coverage: (1) the proportion of study patients with a claim for rifaximin during the study period; and (2)

the proportion of patients with PDC ≥80% by rifaximin. For PDC calculations, the index date was used as the start date, and either the 6-month post-index date or the date of the first hospital admission in the post-index study period was used as the stop date, whichever occurred first.

STATISTICAL ANALYSES

Power Analysis

Using results from Bass et al. (2010),[28] a power analysis was conducted with G*Power software, Version 3.1 to estimate the number of patients needed for detection of the primary outcome measure. Assuming a 1:1 treatment allocation, a total sample size of 452 patients was calculated in order to achieve 80% power with an alpha of 0.05.

Propensity Score Matching

To emulate the properties of a randomized experiment, a cohort of patients matched to each treatment group based on propensity scores (PS) was created, ensuring similar distributions of covariates across treatment groups. To identify which characteristics to include as covariates in the PS-model, a directed acyclic graph was developed using DAGitty Software, Version 3.0.[44] Figure 2.3 shows causal relationships between rifaximin (green node with triangle), the primary outcome measure (blue node), controlled covariates (white nodes), and uncontrolled confounders (red, grey nodes).

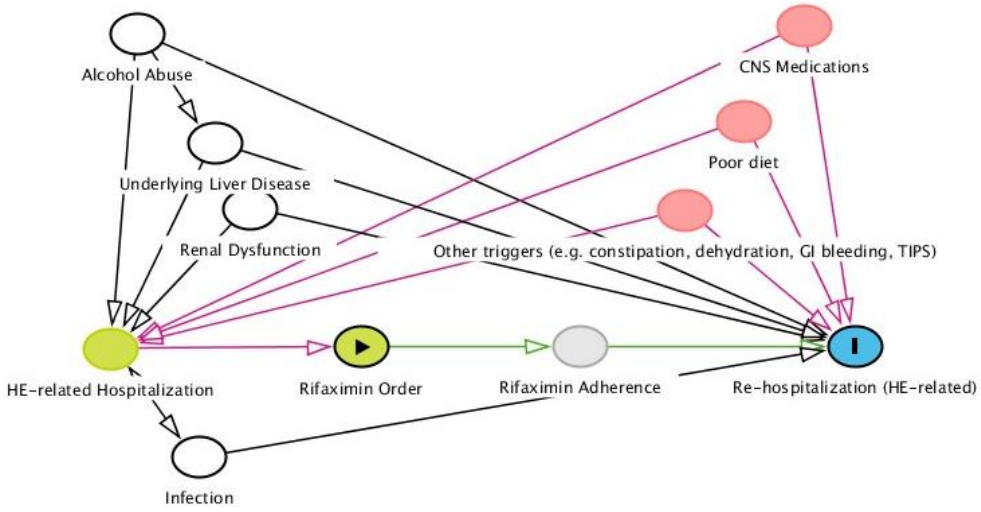


Figure 2.3: Directed Acyclic Graph for Causal Pathways of HE-related Re-hospitalization

While risk factors in the directed acyclic graph such as alcohol abuse, underlying liver disease, renal dysfunction and infection could be measured and controlled for, several other factors such as medications that affect the central nervous system (CNS), poor diet, and other potential triggers are not measured and controlled for, serving as possible confounders in this study. Additionally, adherence to rifaximin was not observable in this study due to the limitations of EHR data.

PS were estimated through logistic multivariable regression using the following list of covariates: age, age category, gender, insurance type, cirrhosis (any), cirrhosis (alcoholic), hepatocellular carcinoma (HCC), hepatitis B, hepatitis C, NAFLD, alcohol abuse, diabetes, renal failure, Elixhauser Comorbidity Index, MELD score, MELD category, Glasgow Coma Scale category, length of stay of the baseline encounter, and elevated WBC. Patients were matched using a pairwise approach and nearest neighbor greedy algorithm.

Statistical Tests

Descriptive statistics (mean, standard deviation (SD), median, interquartile range (IQR), number of observations (n) and proportions) were used to summarize patient and clinical characteristics at baseline. Inferential statistical tests matched to each study objective and hypothesis are listed in Table 2.4:

H_0	Variable	Type	Statistical Test
1.1	Age	Continuous	T-test
1.2	Age category: ≥65 years	Dichotomous	Chi-Square
1.3	Gender	Dichotomous	Chi-Square
1.4	Race	Categorical	Chi-Square
1.5	Ethnicity	Categorical	Chi-Square
1.6	Primary Insurance	Categorical	Chi-Square
1.7a	Comorbidity: Cirrhosis (all)	Dichotomous	Chi-Square
1.7b	Comorbidity: Cirrhosis (alcoholic)	Dichotomous	Chi-Square
1.7c	Comorbidity: Hepatocellular Carcinoma	Dichotomous	Chi-Square
1.7d	Comorbidity: Hepatitis B	Dichotomous	Chi-Square
1.7e	Comorbidity: Hepatitis C	Dichotomous	Chi-Square
1.7f	Comorbidity: NAFLD	Dichotomous	Chi-Square
1.7g	Comorbidity: Alcohol Abuse	Dichotomous	Chi-Square
1.7h	Comorbidity: Diabetes	Dichotomous	Chi-Square
1.7i	Comorbidity: Renal Failure	Dichotomous	Chi-Square
1.8	Elixhauser Comorbidity Index	Ordinal	Mann Whitney
1.9a	Lab: SCr	Continuous	Mann Whitney
1.9b	Lab: Bilirubin	Continuous	Mann Whitney
1.9c	Lab: INR	Continuous	Mann Whitney
1.9d	Lab: Ammonia	Continuous	Mann Whitney
1.9e	Lab: Elevated WBC	Dichotomous	Chi-Square
1.10	MELD score category	Dichotomous	Chi-Square
1.11	Glasgow Coma Scale category	Dichotomous	Chi-Square
1.12a	Prior Medications: Lactulose	Dichotomous	Chi-Square
1.12b	Prior Medications: Rifaximin	Dichotomous	Chi-Square
1.13	Baseline Admit: Length of Stay	Ordinal	Mann Whitney
1.14	Baseline Admit: Lactulose at Discharge	Dichotomous	Chi-Square
2.1	≥1 all-cause hospitalization at 180 days	Dichotomous	Chi-Square
2.2	≥1 liver-related hospitalization at 180 days	Dichotomous	Chi-Square
2.3	≥1 HE-related hospitalization at 180 days	Dichotomous	Chi-Square
2.4	≥1 all-cause hospitalization at 30 days	Dichotomous	Chi-Square
2.5	≥1 liver-related hospitalization at 30 days	Dichotomous	Chi-Square
2.6	≥1 HE-related hospitalization at 30 days	Dichotomous	Chi-Square
2.7	≥1 all-cause ED visit at 180 days	Dichotomous	Chi-Square
2.8	≥1 liver-related ED visit at 180 days	Dichotomous	Chi-Square
2.9	≥1 HE-related ED visit at 180 days	Dichotomous	Chi-Square
2.10	≥1 all-cause ED visit at 30 days	Dichotomous	Chi-Square

H_0	Variable	Type	Statistical Test
2.11	≥1 liver-related ED visit at 30 days	Dichotomous	Chi-Square
2.12	≥1 HE-related ED visit at 30 days	Dichotomous	Chi-Square
2.13	Days to first all-cause hospitalization	Ordinal	Cox Regression / K-M curves
2.14	Days to first liver-related hospitalization	Ordinal	Cox Regression / K-M curves
2.15	Days to first HE-related hospitalization	Ordinal	Cox Regression / K-M curves
2.16	Days to first all-cause ED visit	Ordinal	Cox Regression / K-M curves
2.17	Days to first liver-related ED visit	Ordinal	Cox Regression / K-M curves
2.18	Days to first HE-related ED visit	Ordinal	Cox Regression / K-M curves
3.1	Rifaximin orders vs fills	Dichotomous	Cohen's Kappa
3.2	Rifaximin orders vs. PDC ≥80%	Dichotomous	Cohen's Kappa

Table 2.4. Summary of Hypotheses and Statistical Tests

For analyses of both the full, unmatched cohort and the PS-matched cohort, independent t-tests were used for comparison of means between treatment groups, Mann Whitney U tests were performed for ordinal or continuous but non-normally distributed data, and Chi-square tests were used for proportional comparisons. Baseline characteristics (Objective 1) were evaluated for similarity with $\alpha=0.2$, whereas differences in outcome measures (Objective 2) were assessed with $\alpha=0.05$. Cox proportional hazards models and Kaplan Meier (K-M) curves were used for time-to-event analyses. Lastly, an agreement analysis was conducted for comparison of medication fill measures from pharmacy claims data with treatment group assignments from EHR data. Results for this analysis were summarized descriptively using a frequency table, and level of agreement was assessed with the Cohen's Kappa statistic with a threshold of 0.4 for significant agreement.[45]

Chapter 3: Results

STUDY SAMPLE

A total of 1,541 patients met all study criteria, as shown in Figure 3.1 below:

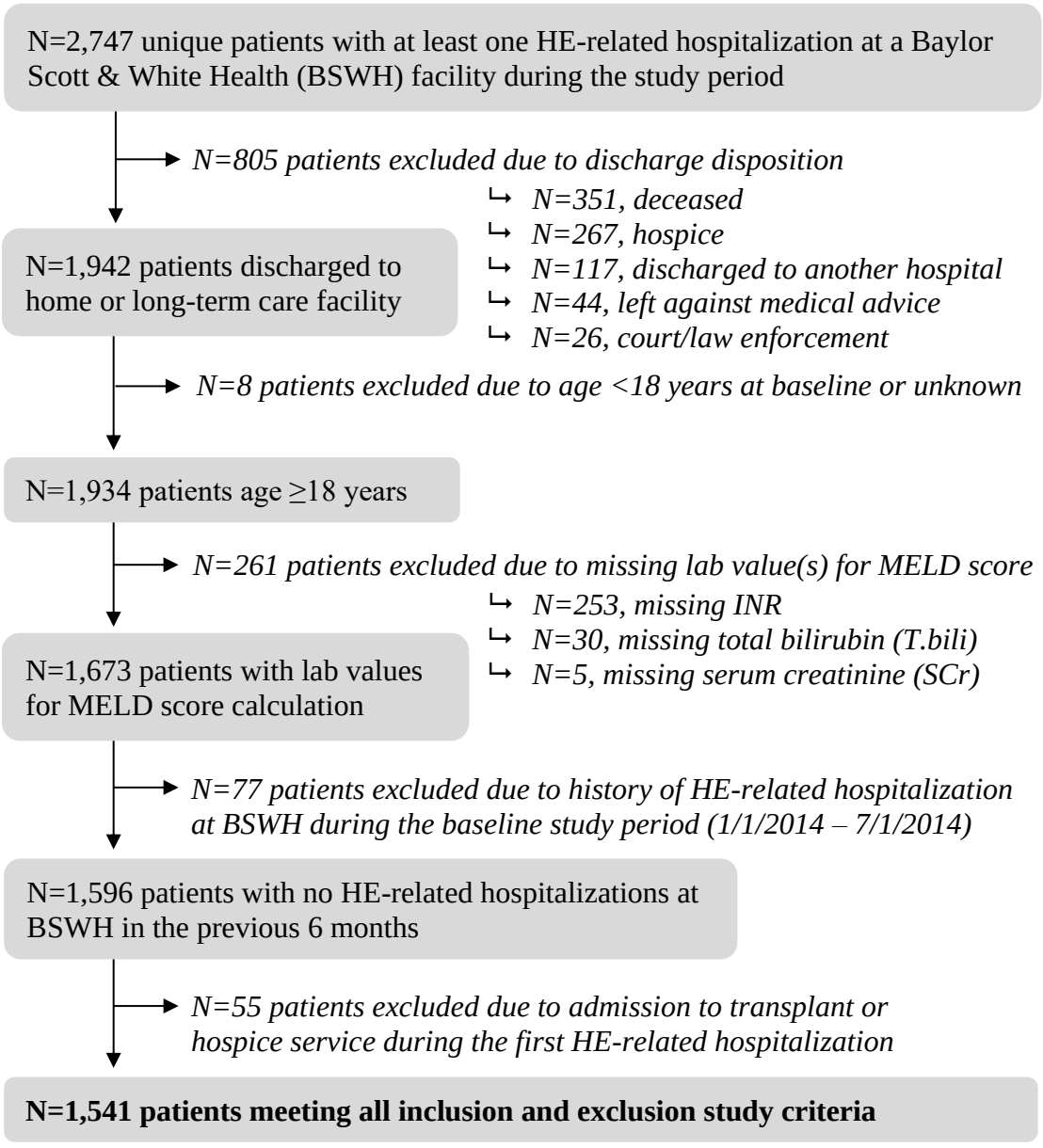


Figure 3.1. Selection Flow Chart

Overall, 2,747 patients with at least one HE-related hospitalization at BSWH during the study period were identified using data from the electronic health record (EHR). Each of the study criteria were applied resulting in exclusion of patients due to discharge disposition (N=805, 29%), missing laboratory values for MELD score calculation (N=261, 10%), history of HE-related hospitalization at BSWH during the baseline study period (N=77, 3%), admission to transplant or hospice service during the first HE-related hospitalization (N=55, 2%), and age less than 18 years (N=8, <1%). The majority of patients excluded due to discharge disposition were deceased (N=351, 44%) or hospice (N=267, 33%), and INR was the most common MELD laboratory value that was missing (N=253, 97%).

Patients were grouped based on the presence (N=351, 'Rifaximin') or absence (N=1,191, 'Control') of an active order for rifaximin documented in the EHR at baseline. Application of the PS-matching methods described in Chapter 2 yielded 347 matched pairs in each treatment group (N=694, total).

BASELINE CHARACTERISTICS

Patient characteristics are summarized by treatment group for both the full study cohort ('Pre-Match') and the PS-matched cohort ('Post-Match') in Table 3.1:

Baseline Characteristic	Pre-Match			Post-Match		
	Rifaximin (N=390)	Control (N=1,151)	*P*-value	Rifaximin (N=347)	Control (N=347)	*P*-value
Age, mean (SD)	60.00 (11.25)	60.27 (12.20)	0.6975	60.19 (11.32)	59.75 (11.78)	0.6176
Age category, N (%)			0.4131			0.9363
< 65 years	260 (66.67%)	741 (64.38%)		228 (65.71%)	227 (65.42%)	
≥ 65 years	130 (33.33%)	410 (35.62%)		119 (34.29%)	120 (34.58%)	
Gender, N (%)			0.4392			0.8196
Female	185 (47.44%)	520 (45.18%)		167 (48.13%)	164 (47.26%)	
Male	205 (52.56%)	631 (54.82%)		180 (51.87%)	183 (52.74%)	
Race, N (%)			0.8164			0.8587
White or Caucasian	320 (82.05%)	949 (82.45%)		288 (83.00%)	284 (81.84%)	
Black or African American	37 (9.49%)	119 (10.34%)		30 (8.65%)	34 (9.80%)	
Other	27 (6.92%)	70 (6.08%)		23 (6.63%)	25 (7.20%)	
Unknown	6 (1.54%)	13 (1.13%)		6 (1.73%)	4 (1.15%)	
Ethnicity, N (%)			0.4727			0.1582
Hispanic or Latinx	80 (20.51%)	265 (23.02%)		74 (21.33%)	86 (24.78%)	
Not Hispanic or Latinx	305 (78.21%)	876 (76.11%)		268 (77.23%)	260 (74.93%)	
Unknown	5 (1.28%)	10 (0.87%)		5 (1.44%)	1 (0.29%)	
Patient Insurance Type, N (%)			0.2215			0.9450
Commercial	92 (23.59%)	255 (22.15%)		82 (23.63%)	80 (23.05%)	
Medicare	195 (50.00%)	556 (48.31%)		175 (50.43%)	174 (50.14%)	
Medicaid	44 (11.28%)	123 (10.69%)		38 (10.95%)	44 (12.68%)	
Other	22 (5.64%)	55 (4.78%)		19 (5.48%)	20 (5.76%)	
Unspecified	37 (9.49%)	162 (14.07%)		33 (9.51%)	29 (8.36%)	
Comorbidity, N (%)						
Cirrhosis (all)	377 (96.67%)	968 (84.10%)	<0.0001	337 (97.12%)	339 (97.69%)	0.6329
Cirrhosis (alcoholic)	192 (49.23%)	518 (45.00%)	0.1479	176 (50.72%)	177 (51.01%)	0.9395
Hepatocellular Carcinoma	25 (6.41%)	102 (8.86%)	0.1281	18 (5.19%)	12 (3.46%)	0.2627

Baseline Characteristic	Pre-Match			Post-Match		
	Rifaximin (N=390)	Control (N=1,151)	*P*-value	Rifaximin (N=347)	Control (N=347)	*P*-value
Hepatitis B	6 (1.54%)	26 (2.26%)	0.3885	4 (1.15%)	5 (1.44%)	0.7372
Hepatitis C	100 (25.64%)	286 (24.85%)	0.7547	88 (25.36%)	86 (24.78%)	0.8610
NAFLD	309 (79.23%)	809 (70.29%)	0.0006	273 (78.67%)	279 (80.40%)	0.5724
Alcohol Abuse	218 (55.90%)	650 (56.47%)	0.8431	197 (56.77%)	201 (57.93%)	0.7588
Diabetes	183 (46.92%)	477 (41.44%)	0.0587	162 (46.69%)	162 (46.69%)	1
Renal Failure	119 (30.51%)	326 (28.32%)	0.4096	104 (29.97%)	107 (30.84%)	0.8045
Elixhauser Comorbidity Index, mean (SD); median (IQR)	53.9 (20.0) 51 (40–68)	52.4 (20.9) 50 (37–67)	0.1392	53.5 (19.4) 51 (40–67)	53.9 (19.9) 52 (39–67)	0.8657
Labs						
Serum Creatinine, mean (SD); median (IQR)	1.3 (1.2) 0.9 (0.7–1.4)	1.3 (1.3) 0.9 (0.7–1.3)	0.3103	1.3 (1.2) 0.9 (0.7–1.3)	1.3 (1.3) 0.9 (0.7–1.3)	0.6311
Bilirubin, mean (SD); median (IQR)	3.7 (5.2) 2.0 (1.1–3.8)	3.4 (4.4) 1.9 (1.0–3.8)	0.2735	3.8 (5.2) 2.1 (1.1–4.0)	3.5 (4.5) 2.1 (1.1–3.7)	0.6557
INR, mean (SD); median (IQR)	1.6 (0.5) 1.4 (1.3–1.7)	1.5 (0.5) 1.4 (1.2–1.7)	0.0169	1.6 (0.5) 1.4 (1.3–1.8)	1.6 (0.5) 1.5 (1.3–1.8)	0.6512
Ammonia, mean (SD); median (IQR)[i]	79.8 (50.1) 66 (46–102.5)	75.1 (56.1) 61 (41–94)	0.0411	80.4 (50.6) 66 (46–102.5)	76.4 (46.9) 61 (42–106)	0.2846
Elevated WBC, N (%)	82 (21.03%)	219 (19.03%)	0.3895	71 (20.46%)	64 (18.44%)	0.5020
MELD score, mean (SD); median (IQR)	14.5 (7.9) 13 (8–18)	13.5 (7.6) 13 (9–19)	0.0924	14.6 (7.8) 13 (9–19)	14.7 (7.3) 14 (10–19)	0.4846
MELD category, N (%)			0.1128			0.8777
≤ 5	35 (8.97%)	153 (13.29%)		31 (8.93%)	25 (7.20%)	
6–10	93 (23.85%)	259 (22.50%)		82 (23.63%)	79 (22.77%)	
11–15	114 (29.49%)	337 (29.28%)		100 (28.82%)	102 (29.39%)	
16–20	64 (16.41%)	213 (18.51%)		60 (17.29%)	73 (21.04%)	
21–25	43 (11.03%)	109 (9.47%)		41 (11.82%)	37 (10.66%)	

Baseline Characteristic	Pre-Match			Post-Match		
	Rifaximin (N=390)	**Control (N=1,151)**	***P*-value**	**Rifaximin (N=347)**	**Control (N=347)**	***P*-value**
26–30	27 (6.92%)	56 (4.87%)		23 (6.63%)	23 (6.63%)	
≥ 31	13 (3.33%)	24 (2.09%)		10 (2.59%)	8 (2.31%)	
Glasgow Coma Scale (GCS), median (IQR)[i]	13.9 (2.3) 15 (14–15)	14.3 (1.8) 15 (14–15)	<0.0001	14.1 (1.9) 15 (14–15)	14.2 (1.9) 15 (14–15)	0.0855
GCS category, N (%)[i]			0.0086			0.8359
Mild (13–15)	309 (86.07%)	965 (91.64%)		308 (88.76%)	311 (89.63%)	
Moderate (9–12)	33 (9.19%)	56 (5.32%)		29 (8.36%)	25 (7.20%)	
Severe (3–8)	17 (4.74%)	32 (3.04%)		10 (2.88%)	11 (3.17%)	
Prior Active Medications, N (%)						
Lactulose	120 (30.77%)	197 (17.12%)	<0.0001	111 (31.99%)	78 (22.48%)	0.0049
Rifaximin	108 (27.69%)	74 (6.43%)	<0.0001	101 (29.11%)	28 (8.07%)	<0.0001
Index HE-related Hospitalization						
Length of Stay, mean (SD); median (IQR)	8.3 (9.6) 6 (3–10)	7.2 (8.1) 5 (3–8)	0.0005	7.8 (7.0) 6 (3–10)	7.7 (8.8) 5 (3–9)	0.0906
HE-related Diagnosis Position, N (%)						
1° – 8° Positions	238 (61.03%)	642 (55.78%)	0.0703	208 (59.94%)	190 (54.76%)	0.1671
1° – 4° Positions	199 (51.03%)	482 (41.88%)	0.0017	172 (49.57%)	151 (43.52%)	0.1100
1° – 2° Positions	178 (45.64%)	415 (36.06%)	0.0008	157 (45.24%)	134 (38.62%)	0.0768
1° Position only	157 (40.26%)	373 (32.41%)	0.0048	140 (40.35%)	124 (35.73%)	0.2109
Lactulose Active at Discharge, N (%)	295 (75.64%)	542 (47.09%)	<0.0001	260 (74.93%)	248 (71.47%)	0.3037

[i] Results are reported using all available values. Missing values are excluded from the denominator unless otherwise reported.

Table 3.1: Baseline Characteristics by Treatment Group and Cohort Type

In the unmatched cohort, patient demographics (age, gender, race, ethnicity, insurance type) were similar across treatment groups. Mean age in both rifaximin and control groups was 60 years, and most patients were less than 65 years old (67% vs. 64%, respectively), male (53% vs. 55%, respectively), white (82%, each), non-Hispanic (78% vs. 76%, respectively), and insured through Medicare (50% vs. 48%, respectively). Using an alpha of 0.2 to determine balance between cohorts, there were significantly higher proportions of patients in the rifaximin group with cirrhosis (all: 97% vs. 84%, $P<0.0001$; alcoholic: 49% vs. 45%, $P=0.1479$), non-alcoholic fatty liver disease (NAFLD: 79% vs. 70%, $P=0.0006$), and diabetes (47% vs. 41%, $P=0.0587$) compared to the control group. However, there were lower proportions of patients in the rifaximin group with hepatocellular carcinoma (6% vs. 9%, $P=0.1281$). The distributions of Elixhauser comorbidity index ($P=0.1392$), MELD score ($P=0.0924$), and length of stay (LOS) of the index HE-related hospitalization (P=0.0005) were skewed higher in the rifaximin group vs. control group, and the distribution of Glasgow Coma Scale (GCS) score was skewed lower ($P<0.0001$) for rifaximin vs. control. Finally, a higher proportion of patients in the rifaximin group received lactulose at discharge (76% vs. 47%; $P<0.0001$) vs. control.

Each of the statistically significant relationships noted in the analysis of the unmatched cohort above were corrected for through PS-matching procedures. Mean age (60 years) and the proportions of patients that were age <65 years (66%), male (52%), white (82%), and insured through Medicare (50%) were similar across treatment groups and to the means and proportions reported in the unmatched cohort. There were no statistically significant relationships between treatment groups and comorbidities, Elixhauser comorbidity index, laboratory values, MELD score, MELD category, and GCS category.

Hypothesis tests and results specific to objective 1 are summarized in Table 3.2:

Objective 1: To evaluate the baseline characteristics of patients following the first qualifying episode of HE.	**Results**	
	Pre-match	**Post-match**
H_0 1.1: The difference in patient age between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 1.2: The difference in proportions of patients by age category between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 1.3: The difference in proportions of patients by gender between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 1.4: The difference in proportions of patients by race category between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 1.5: The difference in proportions of patients by ethnicity between treatment groups is not statistically significant.	Fail to reject	Reject
H_0 1.6: The difference in proportions of patients by primary insurance type between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 1.7: The differences in proportions of patients with select comorbidities at baseline between treatment groups are not statistically significant.	Reject	Fail to reject
H_0 1.8: The difference in patient comorbidity index between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 1.9: The differences in individual laboratory measurements at baseline between treatment groups are not statistically significant.	Reject	Fail to reject
H_0 1.10: The difference in proportions of patients by MELD score category at baseline between treatment groups is not statistically significant	Reject	Fail to reject
H_0 1.11: The difference in proportions of patients by Glasgow Coma Scale category at baseline between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 1.12: The difference in proportions of patients by prior medication use between treatment groups is not statistically significant.	Reject	Reject
H_0 1.13: The difference in length of stay at baseline between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 1.14: The difference in proportion of patients with active lactulose orders at baseline between treatment groups is not statistically significant.	Reject	Fail to reject

Table 3.2: Summary of Results by Hypothesis Test – Objective 1

OUTCOME MEASURES

Hospitalizations and emergency department (ED) visits are summarized by treatment group and cohort type in Table 3.3. Time-to-event analyses are also included for the pre-match cohort in Figure 3.2, and for the PS-matched cohort in Figure 3.3.

Measure, N (%)	Pre-Match			Post-Match		
	Rifaximin (N=390)	**Control (N=1,151)**	***P*-value**	**Rifaximin (N=347)**	**Control (N=347)**	***P*-value**
Patients with ≥1 Hospitalization						
At 180 days post-index						
All-cause	229 (58.72%)	614 (53.34%)	0.0654	202 (58.21%)	196 (56.48%)	0.6451
Liver-related (any position)	225 (57.69%)	561 (48.74%)	0.0022	200 (57.64%)	192 (55.33%)	0.5402
1° – 4° Positions only	178 (45.64%)	413 (35.88%)	0.0006	161 (46.40%)	138 (39.77%)	0.0779
1° – 2° Positions only	144 (36.92%)	350 (30.41%)	0.0172	128 (36.89%)	123 (35.45%)	0.6928
1° Position only	115 (29.49%)	298 (25.89%)	0.1658	101 (29.11%)	105 (30.26%)	0.7396
HE-related (any position)	124 (31.79%)	311 (27.02%)	0.0702	111 (31.99%)	112 (32.28%)	0.9352
1° – 4° Positions only	56 (14.36%)	138 (11.99%)	0.2228	52 (14.99%)	53 (15.27%)	0.9156
1° – 2° Positions only	46 (11.79%)	121 (10.51%)	0.4814	42 (12.10%)	49 (14.12%)	0.4312
1° Position only	39 (10.00%)	113 (9.82%)	0.9168	36 (10.37%)	47 (13.54%)	0.1982
At 30 days post-index						
All-cause	122 (31.28%)	308 (26.76%)	0.0853	107 (30.84%)	101 (29.11%)	0.6191
Liver-related (any position)	118 (30.26%)	280 (24.33%)	0.0208	105 (30.26%)	99 (28.53%)	0.6171
1° – 4° Positions only	81 (20.77%)	190 (16.51%)	0.0560	73 (21.04%)	70 (20.17%)	0.7783
1° – 2° Positions only	66 (16.92%)	153 (13.29%)	0.0760	60 (17.29%)	57 (16.43%)	0.7610
1° Position only	49 (12.56%)	129 (11.21%)	0.4689	46 (13.26%)	49 (14.12%)	0.7404
HE-related (any position)	55 (14.10%)	143 (12.42%)	0.3919	48 (13.83%)	49 (14.12%)	0.9128
1° – 4° Positions only	21 (5.38%)	57 (4.95%)	0.7364	19 (5.48%)	24 (6.92%)	0.4311
1° – 2° Positions only	17 (4.36%)	51 (4.43%)	0.9523	15 (4.32%)	21 (6.05%)	0.3044
1° Position only	15 (3.85%)	45 (3.91%)	0.9553	14 (4.03%)	19 (5.48%)	0.3725
Patients with ≥1 ED Visit						
At 180 days post-index						
All-cause	244 (62.56%)	651 (56.56%)	0.0378	220 (63.40%)	216 (62.25%)	0.7534
Liver-related (any position)	227 (58.21%)	559 (48.57%)	0.0010	206 (59.37%)	198 (57.06%)	0.5381
1° – 4° Positions only	184 (47.18%)	430 (37.36%)	0.0006	169 (48.70%)	150 (43.23%)	0.1478

Measure, N (%)	Pre-Match			Post-Match		
	Rifaximin (N=390)	**Control (N=1,151)**	***P*-value**	**Rifaximin (N=347)**	**Control (N=347)**	***P*-value**
1° – 2° Positions only	137 (35.13%)	365 (31.71%)	0.2134	124 (35.73%)	129 (37.18%)	0.6933
1° Position only	103 (26.41%)	291 (25.28%)	0.6590	93 (26.80%)	104 (29.97%)	0.3544
HE-related (any position)	99 (25.38%)	266 (23.11%)	0.3612	89 (25.65%)	97 (27.95%)	0.4930
1° – 4° Positions only	48 (12.31%)	125 (10.86%)	0.4339	45 (12.97%)	47 (13.54%)	0.8228
1° – 2° Positions only	40 (10.26%)	108 (9.38%)	0.6130	37 (10.66%)	43 (12.39%)	0.4757
1° Position only	34 (8.72%)	100 (8.69%)	0.9856	32 (9.22%)	41 (11.82%)	0.2655
At 30 days post-index						
All-cause	139 (35.64%)	354 (30.76%)	0.0739	123 (35.45%)	120 (34.58%)	0.8113
Liver-related (any position)	128 (32.82%)	293 (25.46%)	0.0048	113 (32.56%)	106 (30.55%)	0.5675
1° – 4° Positions only	89 (22.82%)	207 (17.98%)	0.0361	80 (23.05%)	78 (22.48%)	0.8563
1° – 2° Positions only	61 (15.64%)	171 (14.86%)	0.7081	55 (15.85%)	66 (19.02%)	0.2711
1° Position only	42 (10.77%)	134 (11.64%)	0.6395	39 (11.24%)	51 (14.70%)	0.1751
HE-related (any position)	47 (12.05%)	119 (10.34%)	0.3458	40 (11.53%)	42 (12.10%)	0.8141
1° – 4° Positions only	20 (5.13%)	54 (4.69%)	0.7274	18 (5.19%)	23 (6.63%)	0.4208
1° – 2° Positions only	15 (3.85%)	48 (4.17%)	0.7800	13 (3.75%)	20 (5.76%)	0.2118
1° Position only	14 (3.59%)	42 (3.65%)	0.9569	13 (3.75%)	18 (5.19%)	0.3582
Mortality (all-cause)	72 (18.46%)	229 (19.90%)	0.5370	65 (18.73%)	68 (19.60%)	0.7723

Table 3.3: Healthcare Utilization Measures and Mortality by Treatment Group and Cohort Type

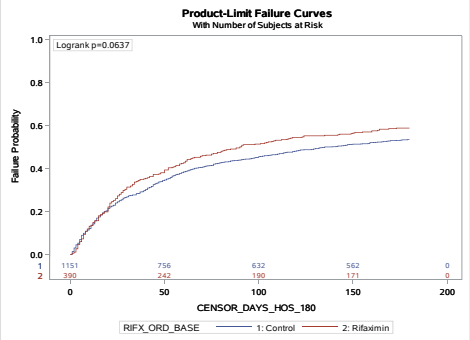
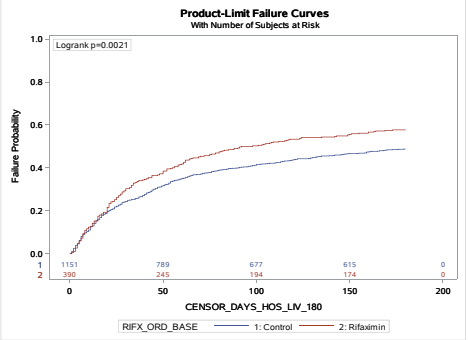
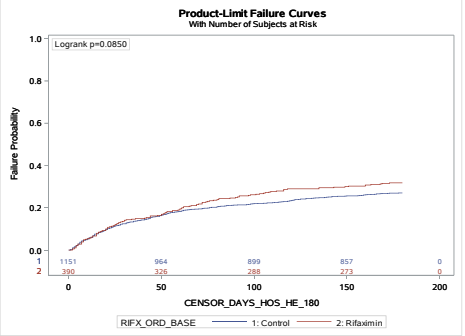
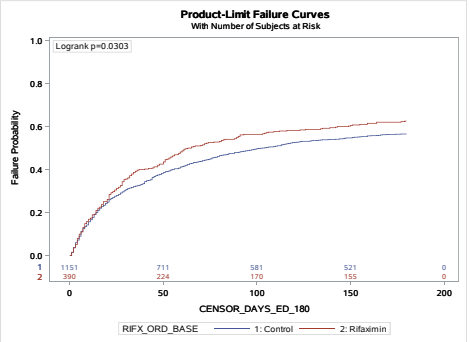
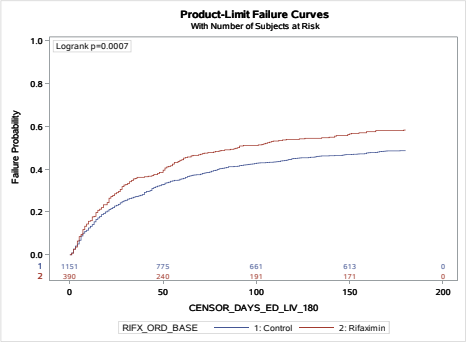
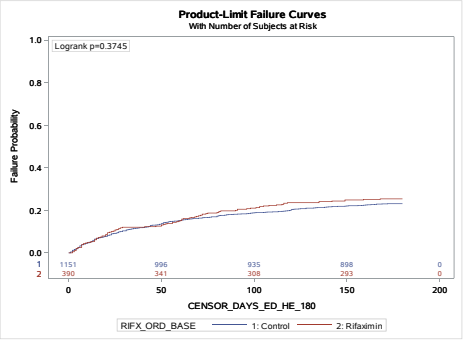
	All-cause	Liver-related (any position)	HE-related (any position)
Hospital	A 	B 	C 
	HR: 1.154; 95% CI [0.991, 1.343]; *P*=0.0650	HR: 1.273; 95% CI [1.091, 1.487]; *P*=0.0022	HR: 1.200; 95% CI [0.975, 1.478]; *P*=0.0858
ED	D 	E 	F 
	HR: 1.176; 95% CI [1.015, 1.362]; *P*=0.0313	HR: 1.304; 95% CI [1.117, 1.521]; *P*=0.0008	HR: 1.110; 95% CI [0.881, 1.398]; *P*=0.3753

Figure 3.2: Kaplan-Meier Curves and Cox Proportional Hazards Ratios for Healthcare Utilization Measures (pre-match)

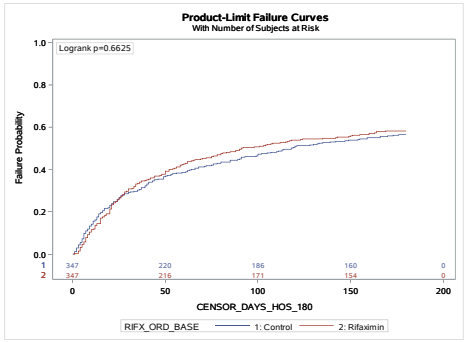
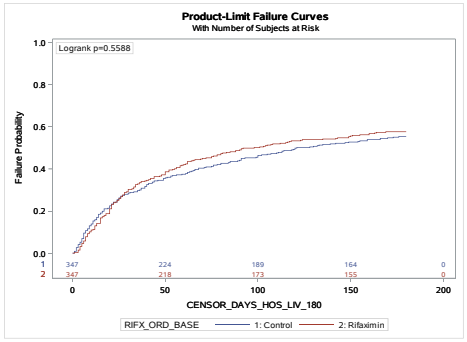
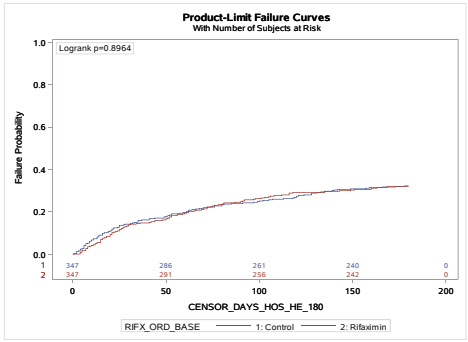
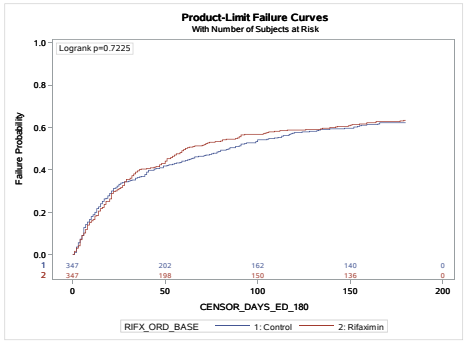
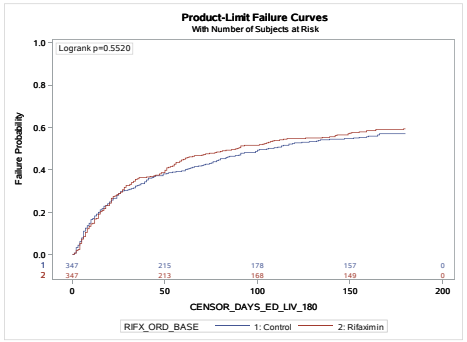
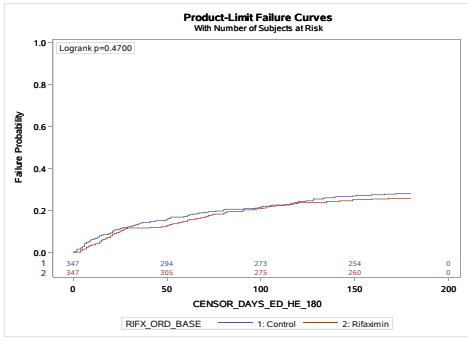
	All-cause	Liver-related (any position)	HE-related (any position)
Hospital	A 	B 	C 
	HR: 1.045; 95% CI [0.858, 1.271]; *P*=0.6638	HR: 1.061; 95% CI [0.870, 1.293]; *P*=0.5605	HR: 0.983; 95% CI [0.756, 1.278]; *P*=0.8966
ED	D 	E 	F 
	HR: 1.034; 95% CI [0.857, 1.248]; *P*=0.7239	HR: 1.061; 95% CI [0.873, 1.289]; *P*=0.5539	HR: 0.900; 95% CI [0.675, 1.199]; *P*=0.4710

Figure 3.3: Kaplan-Meier Curves and Cox Proportional Hazards Ratios for Healthcare Utilization Measures (post-match)

Hospitalizations

In the unmatched cohort (N=390, rifaximin; N=1,151, control), at least one all-cause hospitalization occurred within 180 days in 229 (58.72%) patients in the rifaximin group, compared to 614 (53.34%, *P*=0.0654) patients in the control group. Similarly, there was no statistically significant relationship between treatment group and all-cause hospitalization at 30 days (31.28% vs. 26.76%, *P*=0.0853). There were higher proportions of patients with liver-related hospitalizations using any diagnosis position in the rifaximin group (180 days: 57.69%; 30 days: 30.26%) compared to control (180 days: 48.74%, *P*=0.0006; 30 days: 24.33%, *P*=0.0208); however, these results were sensitive to diagnosis position, as there were no statistically significant relationships in either measure when using diagnoses in the primary position only. HE-related hospitalizations within 180 & 30 days occurred in 124 (31.79%) & 55 (14.10%) patients in the rifaximin group, respectively, and in 311 (27.02%, *P*=0.0702) & 143 (12.42%, *P*=0.3919) patients in the control group, respectively. In the time-to-event analyses, rifaximin was associated with 27% higher risk of liver-related hospitalization (HR: 1.273; 95% CI [1.091, 1.487]; *P*=0.0022) vs. control, but there were no statistically significant differences between treatment groups in risk of all-cause (HR: 1.154; 95% CI [0.991, 1.343]; *P*=0.0650) or HE-related (HR: 1.200; 95% CI [0.975, 1.478]; P=0.0858) hospitalizations.

In the PS-matched cohort (N=347, both groups), there were no statistically significant relationships between treatment groups (rifaximin vs. control) and proportions of patients with all-cause (180 days: 58.21% vs. 56.48%, *P*=0.6451; 30 days: 30.84% vs. 29.11%, *P*=0.6191), liver-related (180 days: 57.64% vs. 55.33%, *P*=0.5402; 30 days: 30.26% vs. 28.53%, *P*=0.6171), or HE-related (180 days: 31.99% vs. 32.28%, *P*=0.9352; 30 days: 13.83% vs. 14.12%, *P*=0.9128) hospitalizations. Similarly, time-to-event analyses

revealed no differences in risk for all-cause (HR: 1.045; 95% CI [0.858, 1.271]; *P*=0.6638), liver-related (HR: 1.061; 95% CI [0.870, 1.293]; *P*=0.5605), or HE-related (HR: 0.983; 95% CI [0.756, 1.278]; *P*=0.8966) hospitalizations in the rifaximin group vs. control.

ED Visits

In the unmatched cohort, there were significantly higher proportions of patients in the rifaximin group vs. control with at least one all-cause ED visit at 180 days (62.56% vs. 56.56%, *P*=0.0378), liver-related ED visit at 180 days (58.21% vs. 48.57%, *P*=0.0010) & 30 days (32.82% vs. 25.46%, *P*=0.0048). However, proportions of patients with at least one ED visit where the liver-related diagnosis was in the primary position did not significantly differ between rifaximin and control groups (180 days: 26.41% vs. 25.28%, *P*=0.6590; 30 days: 10.77% vs. 11.64%, *P*=0.6395). There were also no significant relationships between treatment group and all-cause ED visits at 30 days (35.64% vs. 30.76%, *P*=0.0739), HE-related ED visits at 180 days (25.38% vs. 25.28%, *P*=0.6590), and HE-related ED visits at 30 days (12.05% vs. 10.34%; *P*=0.3458). Rifaximin was associated with 18% higher risk of all-cause ED visits (HR: 1.176; 95% CI [1.015, 1.362]; *P*=0.0313), and 30% higher risk liver-related ED visits (HR: 1.304; 95% CI [1.117, 1.521]; *P*=0.0008) vs. control, but there was no statistically significant difference between treatment groups in risk of HE-related (HR: 1.110; 95% CI [0.881, 1.398]; *P*=0.3753) ED visits.

In the PS-matched cohort, there were no statistically significant relationships between treatment groups (rifaximin vs. control) and all-cause (180 days: 63.40% vs. 62.25%, *P*=0.7534; 30 days: 35.45% vs. 34.58%, *P*=0.8113), liver-related (180 days: 59.37% vs. 57.06%, *P*=0.5381; 30 days: 32.56% vs. 30.55%, *P*=0.5675), or HE-related (180 days: 25.65% vs. 27.95%, *P*=0.4930; 30 days: 11.53% vs. 12.10%, *P*=0.8141). There were also no differences between treatment groups in risk for all-cause (HR: 1.034; 95%

CI [0.857, 1.248]; *P*=0.7239), liver-related (HR: 1.061; 95% CI [0.873, 1.289]; *P*=0.5539), or HE-related (HR: 0.900; 95% CI [0.675, 1.199]; *P*=0.4710) ED visits.

Hypothesis tests and results specific to Objective 2 are summarized in Table 3.4:

Objective 2: To compare healthcare utilization metrics in patients that did or did not receive rifaximin following the first qualifying episode of HE.	**Results**	
	Pre-match	**Post-match**
H_0 2.1: The difference in proportions of patients with at least one all-cause hospitalization at 180 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.2: The difference in proportions of patients with at least one liver-related hospitalization at 180 days between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.3: The difference in proportions of patients with at least one HE-related hospitalization at 180 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.4: The difference in proportions of patients with at least one all-cause hospitalization at 30 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.5: The difference in proportions of patients with at least one liver-related hospitalization at 30 days between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.6: The difference in proportions of patients with at least one HE-related hospitalization at 30 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.7: The difference in proportions of patients with at least one all-cause ED visit at 180 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.8: The difference in proportions of patients with at least one liver-related ED visit at 180 days between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.9: The difference in proportions of patients with at least one HE-related ED visit at 180 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.10: The difference in proportions of patients with at least one all-cause ED visit at 30 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.11: The difference in proportions of patients with at least one liver-related ED visit at 30 days between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.12: The difference in proportions of patients with at least one HE-related ED visit at 30 days between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.13: The difference in time to first all-cause hospitalization between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.14: The difference in time to first liver-related hospitalization between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.15: The difference in time to first HE-related hospitalization between treatment groups is not statistically significant.	Fail to reject	Fail to reject
H_0 2.16: The difference in time to first all-cause ED visit between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.17: The difference in time to first liver-related ED visit between treatment groups is not statistically significant.	Reject	Fail to reject
H_0 2.18: The difference in time to first HE-related ED-visit between treatment groups is not statistically significant.	Fail to reject	Fail to reject

Table 3.4: Summary of Results by Hypothesis Test – Objective 2

Mortality

Of 1,541 patients included in the study, 301 (19.5%) died within 180 days post-index. There were no statistically significant differences between rifaximin vs. control in the proportion of patients that died pre-match (18.5% vs. 19.9%; *P*=0.5370) or post-match (18.7% vs. 19.6%; *P*=0.7723). Time-to-event analysis also showed no significant differences between treatment groups in risk of death pre-match (HR: 0.914; 95% CI [0.701, 1.191]; *P*=0.5053) or post-match (HR: 0.953; 95% CI [0.678, 1.339]; *P*=0.7804).

Adherence

Of 1,541 patients included in the study, 36 (2.3%) patients were continuously enrolled in the Scott & White Health Plan (SWHP) for 6 months pre- and 6 months post-index date. Proportions of patients with medication claims post-index, and proportion of days covered (PDC) ratio ≥ 0.8 are reported by the corresponding absence or presence of orders for each respective medication in Table 3.4 below:

Measure, N (%)	Not Ordered, N (%)	Ordered, N (%)	Total, N (%)	Cohen's Kappa (κ)
Rifaximin (any claim)				0.1702
No Claim	18 (50.00%)	7 (19.44%)	25 (69.44%)	
Claim	6 (16.67%)	5 (13.89%)	11 (30.56%)	
Total	24 (66.67%)	12 (33.33%)	36 (100%)	
Rifaximin (PDC)				0.1000
<80%	22 (61.11%)	10 (27.78%)	32 (88.89%)	
≥80%	2 (5.56%)	2 (5.56%)	4 (11.11%)	
Total	24 (66.67%)	12 (33.33%)	36 (100%)	
Lactulose (any claim)				0.1818
No Claim	8 (22.22%)	11 (30.56%)	19 (52.78%)	
Claim	4 (11.11%)	13 (36.11%)	17 (47.22%)	
Total	12 (33.33%)	24 (66.67%)	36 (100%)	
Lactulose (PDC)				-0.0286
<80%	11 (30.56%)	23 (63.89%)	34 (94.44%)	
≥80%	1 (2.78%)	1 (2.78%)	2 (5.56%)	

Total	12 (33.33%)	24 (66.67%)	36 (100%)	

Green = agreement, Red = disagreement

Table 3.5: Medication Order vs. Medication Claims Data in SWHP Study Patients

There were 12 (33.33%) patients with active rifaximin orders, 11 (30.56%) patients with at least one medication claim for rifaximin (63.89% agreement, κ=0.1702), and 4 (11.11%) patients with PDC $\geq$ 0.8 (66.67% agreement, κ=0.1000). Of the 11 patients that had a claim for rifaximin, 4 (36.37%) patients were adherent with PDC $\geq$ 0.8. For lactulose, there were 24 (66.67%) patients with active medication orders, 17 (47.22%) patients with at least one medication claim (58.33% agreement, κ=0.1818), and 2 (5.56%) patients with PDC $\geq$ 0.8 (33.33% agreement, κ=-0.0286). Of the 17 patients that had a claim for lactulose, 2 (11.76%) patients were adherent with PDC $\geq$ 0.8.

Hypothesis tests and results specific to Objective 3 are summarized in Table 3.6:

Objective 3: To assess the accuracy of using EHR data to define medication use in patients prescribed rifaximin as prophylaxis for HE.	**Results**
H_0 3.1: The difference in proportions of patients with rifaximin ordered vs. filled data is not statistically significant.	Reject
H_0 3.2: The difference in proportions of patients with rifaximin ordered vs. proportion of days covered by rifaximin ≥80% is not statistically significant.	Reject

Table 3.6: Summary of Results by Hypothesis Test – Objective 3

SENSITIVITY ANALYSES

Two sensitivity analyses were conducted to describe how HE-related diagnosis position used for inclusion criteria, and crossover between treatment groups impact healthcare utilization measures. Result tables for these analyses are in Appendix B.

Diagnosis Position

Five scenarios were evaluated with increasing levels of restriction on position required for the HE-related diagnosis used for study inclusion. This yielded the following number of study patients pre-match and post-match:

(1) any position (N=1,541, pre-; N=694, post-),

(2) positions 1–8 only (N=880, pre-; N=390, post-),

(3) positions 1–4 only (N=681, pre-; N=320, post-),

(4) primary or secondary positions only (N=593, pre-; N=288, post-), and

(5) primary position only (N=530, pre-; N=256, post-).

Increasing levels of restriction on diagnosis position did not produce substantially different results in the proportions of patients with at least one event. The largest ranges in proportions pre-match were found in HE-related hospitalizations at 180 days (28.23–32.64%), liver-related ED visits at 180 days (51.01–56.04%), and HE-related ED-visits at 180 days (23.69–28.68%), each trending higher with increasing levels of restriction. Across each of the PS-matched cohorts, the largest ranges in proportions included all-cause hospitalizations at 30 days (24.22–29.97%), liver-related hospitalizations at 30 days (24.22–29.39%), and liver-related ED visits at 30 days (27.34–31.56%), each trending lower with increasing levels of restriction.

Crossover

Crossover from control to rifaximin, defined as a new order for rifaximin after the index date but prior to any hospitalization or ED-visit, was detected in 63 (5.5%) patients in the control group. In patients where crossover was detected, time to crossover was 1–7 days for 12 (19%) patients, 8–30 days for 24 (38%) patients, 31–90 days for 19 (30%) patients, and 91–180 days for 8 (19%) patients. With re-assignment of these patients to the rifaximin group, pre-match, liver-related, 30-day hospitalizations (rifaximin: 27.59%, control 25.09%, *P*=0.3066) and ED visits (rifaximin: 29.80%, control: 26.29%, *P*=0.1584) were no longer significantly associated with treatment group. Otherwise, there were no changes from the primary analysis in statistical significance between treatment groups.

Chapter 4: Discussion

DISCUSSION

This retrospective cohort study evaluated the impact of active rifaximin medication orders on healthcare utilization measures in real-world patients following discharge from hospitalization due to hepatic encephalopathy (HE). Although several baseline characteristics were unbalanced across treatment groups in the full study cohort, propensity score (PS) matching techniques controlled for these differences while also including enough patients to meet 80% power. Results from the PS-matched analysis showed no statistically significant differences in all-cause, liver-related, or HE-related hospitalizations or ED visits at either 30 or 180 days. These results were not sensitive to different criteria for diagnosis position (used either for study inclusion or outcome measurement) or re-assignment based on detectable crossover. However, there was little to no agreement between medication orders and medication claims or adherence, emphasizing the importance of distinguishing between medication orders and medication use when interpreting results from the analysis of healthcare utilization measures.

Compared to the pivotal, randomized controlled trial that demonstrated efficacy of rifaximin in reducing HE-related hospitalizations,[28] patients included in the PS-matched cohort of this study on average were older (60 vs. 56 years) and had more advanced liver disease (MELD ≥26: 11% vs. 0%). Patients with gastrointestinal bleeding, renal or respiratory insufficiency, anemia, electrolyte abnormality, infection, or spontaneous bacterial peritonitis, were excluded from the clinical trial, but were not excluded from this study. The overall presence of HE-related hospitalizations at 168 days in the clinical trial was approximately 18%, which was within the range of HE-related hospitalization rates at 180 days observed in this study (12%, primary position only; 32%, any position). However,

differences in HE-related hospitalizations between treatment groups observed in clinical trials was not seen in this study, which could potentially be explained by lack of access or poor adherence to rifaximin as seen in the subgroup of patients where medication claims data could be assessed. A high comorbidity burden, as was observed in this study sample, is also likely to result in high all-cause hospitalization rate, which was not evaluated in the clinical trial.

While adherence to rifaximin was efficacious in specific patient populations in clinical trial settings, these same results may not always be seen in broader, real-world populations. Cost-effectiveness analyses that rely on these results as assumptions are likely to overestimate the potential cost-savings opportunity from decreased hospitalizations. As such, it is important to consider the complex nature of this disease state and incorporate a wide range of possible outcomes when conducting cost-effectiveness analyses.

Pharmacists are uniquely positioned to help improve patient outcomes in patients with HE. While medications may be ordered at discharge, timely completion of prior authorizations are needed to ensure patient access to therapy. Effective medication counseling at discharge can improve patient education and adherence, increasing the number of patients that receive maximal benefit from medications. Future research should focus on patient-specific factors and patient education strategies that lead to higher adherence rates to rifaximin and improved outcomes in real-world settings.

LIMITATIONS

Due to the retrospective design of the study, there are several potential sources of bias, including poor control over the exposure factor, covariates, and potential confounders. Because this study primarily relies on EHR data, hospitalizations and ED visits occurring outside of the BSWH system are not captured. Medication orders documented in the EHR do not necessarily correlate with medication fills or adherence. Errors made in the selection and positioning of diagnosis codes in the EHR may lead to imprecisions in patient selection and/or outcome measures, though sensitivity analyses showed little impact of different positions of diagnosis codes on differences in outcome measures between treatment groups. Lastly, results of this study may not be generalizable to broader populations outside of the BSWH system.

CONCLUSIONS

After controlling for measurable covariates, patients discharged from an HE-related hospitalization on average experienced no statistically significant differences in all-cause, liver-related, or HE-related hospitalizations, ED visits at 30 or 180 days, or mortality rates with or without a rifaximin order at discharge. While rifaximin was shown to be efficacious in clinical trials, patients with greater disease burden as well as barriers to adherence may limit the cost-effectiveness of rifaximin in real-world settings. Future research should incorporate real-world data in cost-effectiveness analyses and assess the impact of patient-specific factors and patient education strategies on patient outcomes and adherence.

Appendix A: Diagnosis Code Lists

Comorbidity	Code List
HE-related Diagnoses	**ICD-9-CM**: 572.2 **ICD-10-CM**: K72.10, K72.11, K72.90, K72.91
Liver-related Diagnoses	**ICD-9-CM**: 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7 **ICD-10-CM**: B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4
Cirrhosis, any	**ICD-9-CM**: 571.2, 571.5 **ICD-10-CM**: K70.3x, K71.7, K74.6x, P78.81
Cirrhosis, alcoholic	**ICD-9-CM**: 571.2 **ICD-10-CM**: K70.3x
Hepatocellular Carcinoma	**ICD-9-CM**: 155.0 **ICD-10-CM**: C22.0
Hepatitis B	**ICD-9-CM**: 070.2x, 070.3x **ICD-10-CM**: B16.x, B18.0, B18.1, B19.1x
Hepatitis C	**ICD-9-CM**: 070.41, 070.44, 070.51, 070.54, 070.7x **ICD-10-CM**: B17.1x, B18.2, B19.2x
NAFLD/NASH	**ICD-9-CM**: 571.5, 571.8, 571.9 **ICD-10-CM**: K75.81, K76.0
Alcohol Abuse	**ICD-9-CM**: 265.2, 291.1–291.3, 291.5–291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0–571.3, 980.x, V11.3 **ICD-10-CM**: F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1
Diabetes	**ICD-9-CM**: 250.x **ICD-10-CM**: E10–E14
Renal Failure	**ICD-9-CM**: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x **ICD-10-CM**: I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2

Table A.1: Diagnosis Code List for Baseline Comorbidities

Comorbidity	Code List
AIDS/HIV	**ICD-9-CM**: 042.x–044.x **ICD-10-CM**: B20.x–B22.x, B24.x
Alcohol Abuse	**ICD-9-CM**: 265.2, 291.1–291.3, 291.5–291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0–571.3, 980.x, V11.3 **ICD-10-CM**: F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1
Deficiency Anemia	**ICD-9-CM**: 280.1–280.9, 281.x **ICD-10-CM**: D50.8, D50.9, D51.x–D53.x
Rheumatoid Arthritis/Collagen Vascular Diseases	**ICD-9-CM**: 446.x, 701.0, 710.0–710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30 **ICD-10-CM**: L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0 - M31.3, M32.x - M35.x, M45.x, M46.1, M46.8, M46.9
Blood Loss Anemia	**ICD-9-CM**: 280.0 **ICD-10-CM**: D50.0
Congestive Heart Failure	**ICD-9-CM**: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4–425.9, 428.x **ICD-10-CM**: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43.x, I50.x, P29.0
Chronic Pulmonary Disease	**ICD-9-CM**: 416.8, 416.9, 490.x–505.x, 506.4, 508.1, 508.8 **ICD-10-CM**: I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Coagulopathy	**ICD-9-CM**: 286.x, 287.1, 287.3–287.5 **ICD-10-CM**: D65–D68.x, D69.1, D69.3–D69.6
Depression	**ICD-9-CM**: 296.2, 296.3, 296.5, 300.4, 309.x, 311 **ICD-10-CM**: F20.4, F31.3 - F31.5, F32.x, F33.x, F34.1, F41.2, F43.2
Diabetes, uncomplicated	**ICD-9-CM**: 250.0 - 250.3 **ICD-10-CM**: E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes, complicated	**ICD-9-CM**: 250.4–250.9 **ICD-10-CM**: E10.2–E10.8, E11.2–E11.8, E12.2–E12.8, E13.2–E13.8, E14.2–E14.8
Drug Abuse	**ICD-9-CM**: 292.x, 304.x, 305.2–305.9, V65.42 **ICD-10-CM**: F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2
Hypertension, complicated	**ICD-9-CM**: 402.x–405.x **ICD-10-CM**: I11.x–I13.x, I15.x
Hypothyroidism	**ICD-9-CM**: 240.9, 243.x, 244.x, 246.1, 246.8 **ICD-10-CM**: E00.x–E03.x, E89.0
Liver Disease	**ICD-9-CM**: 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0–456.2, 570.x, 571.x, 572.2–572.8, 573.3, 573.4, 573.8, 573.9, V42.7 **ICD-10-CM**: B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3–K71.5, K71.7, K72.x–K74.x, K76.0, K76.2–K76.9, Z94.4

Lymphoma	**ICD-9-CM**: 200.x–202.x, 203.0, 238.6 **ICD-10-CM**: C81.x–C85.x, C88.x, C96.x, C90.0, C90.2
Fluid and Electrolyte Disorders	**ICD-9-CM**: 253.6, 276.x **ICD-10-CM**: E22.2, E86.x, E87.x
Metastatic Cancer	**ICD-9-CM**: 196.x–199.x **ICD-10-CM**: C77.x–C80.x
Other Neurological Disorders	**ICD-9-CM**: 331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x - 335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3 **ICD-10-CM**: G10.x–G13.x, G20.x–G22.x, G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x–G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x
Obesity	**ICD-9-CM**: 278.0 **ICD-10-CM**: E66.x
Paralysis	**ICD-9-CM**: 334.1, 342.x, 343.x, 344.0 - 344.6, 344.9 **ICD-10-CM**: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
Peripheral Vascular Disorders	**ICD-9-CM**: 093.0, 437.3, 440.x, 441.x, 443.1–443.9, 447.1, 557.1, 557.9, V43.4 **ICD-10-CM**: I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Psychoses	**ICD-9-CM**: 293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x **ICD-10-CM**: F20.x, F22.x–F25.x, F28.x, F29.x, F30.2, F31.2, F31.5
Pulmonary Circulation Disorders	**ICD-9-CM**: 415.0, 415.1, 416.x, 417.0, 417.8, 417.9 **ICD-10-CM**: I26.x, I27.x, I28.0, I28.8, I28.9
Renal Failure	**ICD-9-CM**: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x **ICD-10-CM**: I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Solid Tumor without Metastasis	**ICD-9-CM**: 140.x–172.x, 174.x–195.x **ICD-10-CM**: C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C97.x
Peptic Ulcer Disease	**ICD-9-CM**: 531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9 **ICD-10-CM**: K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9
Valvular Disease	**ICD-9-CM**: 093.2, 394.x–397.x, 424.x, 746.3–746.6, V42.2, V43.3 **ICD-10-CM**: A52.0, I05.x–I08.x, I09.1, I09.8, I34.x–I39.x, Q23.0–Q23.3, Z95.2–Z95.4
Weight Loss	**ICD-9-CM**: 260.x–263.x, 783.2, 799.4 **ICD-10-CM**: E40.x–E46.x, R63.4, R64

Table A.2: Diagnosis Code List for Elixhauser Comorbidity Index [Adapted][46]

Appendix B: Sensitivity Analysis Results

Measure, N (%)	Pre-Match, Baseline HE Diagnosis Position				
	Any Position (N=1,541)	**1° – 8° Positions (N=880)**	**1° – 4° Positions (N=681)**	**1° – 2° Positions (N=593)**	**1° Position only (N=530)**
Patients with ≥1 Hospitalization					
At 180 days post-index					
All-cause	843 (54.70%)	465 (52.84%)	368 (54.04%)	332 (55.99%)	298 (56.23%)
Liver-related (any position)	786 (51.01%)	442 (50.23%)	355 (52.13%)	322 (54.30%)	289 (54.53%)
HE-related (any position)	435 (28.23%)	256 (29.09%)	211 (30.98%)	188 (31.70%)	173 (32.64%)
At 30 days post-index					
All-cause	430 (27.90%)	221 (25.11%)	171 (25.11%)	153 (25.80%)	136 (25.66%)
Liver-related (any position)	398 (25.83%)	211 (23.98%)	166 (24.38%)	149 (25.13%)	135 (25.47%)
HE-related (any position)	198 (12.85%)	106 (12.05%)	85 (12.48%)	74 (12.48%)	68 (12.83%)
Patients with ≥1 ED Visit					
At 180 days post-index					
All-cause	895 (58.08%)	505 (57.39%)	405 (59.47%)	363 (61.21%)	328 (61.89%)
Liver-related (any position)	786 (51.01%)	451 (51.25%)	361 (53.01%)	328 (55.31%)	297 (56.04%)
HE-related (any position)	365 (23.69%)	220 (25.00%)	184 (27.02%)	166 (27.99%)	152 (28.68%)
At 30 days post-index					
All-cause	493 (31.99%)	261 (29.66%)	202 (29.66%)	181 (30.52%)	162 (30.57%)
Liver-related (any position)	421 (27.32%)	229 (26.02%)	177 (25.99%)	159 (26.81%)	142 (26.79%)
HE-related (any position)	166 (10.77%)	92 (10.45%)	76 (11.16%)	67 (11.30%)	61 (11.51%)

Table B.1. Healthcare Utilization Measures by Baseline HE-related Diagnosis Position (Pre-Match)

Measure, N (%)	Post-Match*, Baseline HE Diagnosis Position				
	Any Position (N=694)	**1° – 8° Positions (N=390)**	**1° – 4° Positions (N=320)**	**1° – 2° Positions (N=288)**	**1° Position only (N=256)**
Patients with ≥1 Hospitalization					
At 180 days post-index					
All-cause	398 (57.35%)	217 (55.64%)	173 (54.06%)	160 (55.56%)	146 (57.03%)
Liver-related (any position)	392 (56.48%)	213 (54.62%)	171 (53.44%)	158 (54.86%)	145 (56.64%)
HE-related (any position)	223 (32.13%)	123 (31.54%)	104 (32.50%)	91 (31.60%)	82 (32.03%)
At 30 days post-index					
All-cause	208 (29.97%)	107 (27.44%)	81 (25.31%)	70 (24.31%)	62 (24.22%)
Liver-related (any position)	204 (29.39%)	105 (26.92%)	81 (25.31%)	69 (23.96%)	62 (24.22%)
HE-related (any position)	97 (13.98%)	50 (12.82%)	43 (13.44%)	31 (10.76%)	31 (12.11%)
Patients with ≥1 ED Visit					
At 180 days post-index					
All-cause	436 (62.82%)	241 (61.79%)	201 (62.81%)	184 (63.89%)	170 (66.41%)
Liver-related (any position)	404 (58.21%)	223 (57.18%)	183 (57.19%)	170 (59.03%)	156 (60.94%)
HE-related (any position)	186 (26.80%)	102 (26.15%)	95 (29.69%)	82 (28.47%)	75 (29.30%)
At 30 days post-index					
All-cause	243 (35.01%)	129 (33.08%)	104 (32.50%)	189 (30.90%)	83 (32.42%)
Liver-related (any position)	219 (31.56%)	114 (29.23%)	90 (28.13%)	77 (26.74%)	70 (27.34%)
HE-related (any position)	82 (11.82%)	40 (10.26%)	41 (12.81%)	30 (10.42%)	29 (11.33%)

*Note: Separate PS-Matching procedures were performed on each cohort by rule for diagnosis position (from Table 3)

Table B.2. Healthcare Utilization Measures by Baseline HE-related Diagnosis Position (Post-Match)

Measure, N (%)	Time (Days) from Index Date to Rifaximin Order				Total (N=63)
	At 1–7 days (N=12)	At 8–30 days (N=24)	At 31–90 days (N=19)	At 91–180 days (N=8)	
Patients with ≥1 Hospitalization					
At 180 days post-index					
All-cause	6 (50.00%)	13 (54.17%)	8 (42.11%)	0 (0.00%)	27 (42.86%)
Liver-related (any position)	6 (50.00%)	13 (54.17%)	7 (36.84%)	0 (0.00%)	26 (41.27%)
HE-related (any position)	6 (50.00%)	5 (20.83%)	4 (21.05%)	0 (0.00%)	15 (23.81%)
At 30 days post-index					
All-cause	2 (16.67%)	5 (20.83%)	0 (0.00%)	0 (0.00%)	7 (11.11%)
Liver-related (any position)	2 (16.67%)	5 (20.83%)	0 (0.00%)	0 (0.00%)	7 (11.11%)
HE-related (any position)	1 (8.33%)	1 (4.17%)	0 (0.00%)	0 (0.00%)	2 (3.17%)
Patients with ≥1 ED Visit					
At 180 days post-index					
All-cause	5 (41.67%)	12 (50.00%)	7 (36.84%)	0 (0.00%)	24 (38.10%)
Liver-related (any position)	5 (41.67%)	12 (50.00%)	7 (36.84%)	0 (0.00%)	24 (38.10%)
HE-related (any position)	4 (33.33%)	4 (16.67%)	4 (21.05%)	0 (0.00%)	12 (19.05%)
At 30 days post-index					
All-cause	2 (16.67%)	5 (20.83%)	0 (0.00%)	0 (0.00%)	7 (11.11%)
Liver-related (any position)	2 (16.67%)	5 (20.83%)	0 (0.00%)	0 (0.00%)	7 (11.11%)
HE-related (any position)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Table B.3: Healthcare Utilization Measures in All Study Patients with Crossover from Control Group to Rifaximin Group

Measure, N (%)	Pre-Match			Post-Match		
	Rifaximin (N=453)	**Control (N=1,088)**	***P*-value**	**Rifaximin (N=401)**	**Control (N=401)**	***P*-value**
Patients with ≥1 Hospitalization						
At 180 days post-index						
All-cause	256 (56.51%)	587 (53.95%)	0.3577	225 (56.11%)	225 (56.11%)	1
Liver-related (any position)	251 (55.41%)	535 (49.17%)	0.0257	221 (55.11%)	217 (54.11%)	0.7766
1° – 4° Positions only	196 (43.27%)	395 (36.31%)	0.0104	177 (44.14%)	157 (39.15%)	0.1520
1° – 2° Positions only	160 (35.32%)	334 (30.70%)	0.0766	143 (35.66%)	129 (32.17%)	0.2964
1° Position only	130 (28.70%)	283 (26.01%)	0.2780	115 (28.68%)	112 (27.93%)	0.8141
HE-related (any position)	139 (30.68%)	296 (27.21%)	0.1670	123 (30.67%)	125 (31.17%)	0.8786
1° – 4° Positions only	62 (13.69%)	132 (12.13%)	0.4021	57 (14.21%)	61 (15.21%)	0.6901
1° – 2° Positions only	52 (11.48%)	115 (10.57%)	0.6009	47 (11.72%)	56 (13.97%)	0.3422
1° Position only	45 (9.93%)	107 (9.83%)	0.9525	41 (10.22%)	51 (12.72%)	0.2678
At 30 days post-index						
All-cause	129 (28.48%)	301 (27.67%)	0.7463	114 (28.43%)	109 (27.18%)	0.6935
Liver-related (any position)	125 (27.59%)	273 (25.09%)	0.3066	111 (27.68%)	105 (26.18%)	0.6329
1° – 4° Positions only	84 (18.54%)	187 (17.19%)	0.5243	76 (18.95%)	71 (17.71%)	0.6482
1° – 2° Positions only	68 (15.01%)	151 (13.88%)	0.5619	62 (15.46%)	55 (13.72%)	0.4838
1° Position only	50 (11.04%)	128 (11.76%)	0.6841	47 (11.72%)	46 (11.47%)	0.9122
HE-related (any position)	57 (12.58%)	141 (12.96%)	0.8404	49 (12.22%)	55 (13.72%)	0.5283
1° – 4° Positions only	21 (4.64%)	57 (5.24%)	0.6226	19 (4.74%)	25 (6.23%)	0.3522
1° – 2° Positions only	17 (3.75%)	51 (4.69%)	0.4157	15 (3.74%)	24 (5.99%)	0.1395
1° Position only	15 (3.31%)	45 (4.14%)	0.4458	14 (3.49%)	20 (4.99%)	0.2930
Patients with ≥1 ED Visit						
At 180 days post-index						
All-cause	268 (59.16%)	627 (57.63%)	0.5786	241 (60.10%)	244 (60.85%)	0.8285
Liver-related (any position)	251 (55.41%)	535 (49.17%)	0.0257	226 (56.36%)	223 (55.61%)	0.8310
1° – 4° Positions only	202 (44.59%)	412 (37.87%)	0.0140	184 (45.89%)	169 (42.14%)	0.2860

Measure, N (%)	Pre-Match			Post-Match		
	Rifaximin (N=453)	Control (N=1,088)	*P*-value	Rifaximin (N=401)	Control (N=401)	*P*-value
1° – 2° Positions only	153 (33.77%)	349 (32.08%)	0.5171	138 (34.41%)	139 (34.66%)	0.9408
1° Position only	118 (26.05%)	276 (25.37%)	0.7801	106 (26.43%)	111 (27.68%)	0.6911
HE-related (any position)	111 (24.50%)	254 (23.35%)	0.6263	100 (24.94%)	108 (26.93%)	0.5192
1° – 4° Positions only	54 (11.92%)	119 (10.94%)	0.5776	50 (12.47%)	56 (13.97%)	0.5316
1° – 2° Positions only	46 (10.15%)	102 (9.38%)	0.6361	42 (10.47%)	51 (12.72%)	0.3209
1° Position only	40 (8.83%)	94 (8.64%)	0.9039	37 (9.23%)	47 (11.72%)	0.2488
At 30 days post-index						
All-cause	146 (32.23%)	347 (31.89%)	0.8974	131 (32.67%)	134 (33.42%)	0.8218
Liver-related (any position)	135 (29.80%)	286 (26.29%)	0.1584	120 (29.93%)	114 (28.43%)	0.6412
1° – 4° Positions only	93 (20.53%)	203 (18.66%)	0.3955	84 (20.95%)	80 (19.95%)	0.7262
1° – 2° Positions only	64 (14.13%)	168 (15.44%)	0.5114	58 (14.46%)	67 (16.71%)	0.3809
1° Position only	45 (9.93%)	131 (12.04%)	0.2362	42 (10.47%)	53 (13.22%)	0.2294
HE-related (any position)	47 (10.38%)	119 (10.94%)	0.7457	40 (9.98%)	48 (11.97%)	0.3661
1° – 4° Positions only	20 (4.42%)	54 (4.96%)	0.6466	18 (4.49%)	24 (5.99%)	0.3416
1° – 2° Positions only	15 (3.31%)	48 (4.41%)	0.3203	13 (3.24%)	23 (5.74%)	0.0881
1° Position only	14 (3.09%)	42 (3.86%)	0.4619	13 (3.24%)	20 (4.99%)	0.2133

Table B.4: Healthcare Utilization Measures by Treatment Group (Adjusted for Crossover) and Cohort Type

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